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SOME REMARKS ON THERAPY FOR ANEMIA*

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I AM sincerely appreciative of the honor bestowed on me by the invitation to deliver this oration. As you are aware, my distinguished predecessors have annually instructed and entertained you with words both wise and charming. I wish, especially at this preprandial hour, that I were able to do so. Lacking such gifts, however, I have believed that in accepting this honor it would be a more suitable expression of appreciation were I to speak of matters of detail with which I have some experience than to discourse, perhaps naïvely, on a more general theme.

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The remarkable advances in the treatment of anemia of the past decade and a half, when contrasted with the yet unscalable obstacles, perhaps justify an attempt at a realistic appraisal of the possibilities and limitations of existing therapy. Today, five general methods of treatment of varying effectiveness and permanence are clearly discernible. Thus, there are substitution therapy for nutritional deficiency or for dysfunction of the endocrine system, chemotherapy, splenectomy and irradiation. Finally, on its own merits and also as a means of preparation for some other form of therapy, there is transfusion.

SUBSTITUTION THERAPY

Starting with the pioneer clinical observations of Minot and Murphy in 1926, the effectiveness of liver and later of stomach preparations in the treatment of patients with nutritional types of macrocytic anemia has become thoroughly established. In this locality, the conditions amenable to such therapy are usually Addisonian pernicious anemia and that of pregnancy. With the further exception of certain rare cases of nutritional macrocytic anemia, usually due to intestinal disturbances, all types of anemia fail entirely to respond to such preparations. Valuable contributions to the practical development of the present effective therapeutic products have been made by both university and commercial research groups. Since the amount of active material remaining in the finished product depends on the efficiency of the method of manufacture, it seems unwise and uneconomical for physicians to prescribe products whose potency is defined only in terms of the amounts of tissue with which the manufacturer started his process. The obvious and satisfactory alternative definition of potency in terms of the amount of effective material in the final product is currently described in *U.S.P.* units for all antianemia remedies accepted by the *United States Pharmacopoeia* or the Council on Pharmacy and Chemistry of the American Medical Association.

Active commercial preparations of the liver for oral or parenteral use, and of the stomach or of the stomach and the liver potentiated by incubation for oral use, are available. Because in the average patient the effectiveness of a given liver preparation is from sixty to one hundred times as great when given parenterally as when taken by mouth, the former route provides a distinctly more economical manner of administration. The small volume of material to be injected (several commercial preparations contain at least 15 *U.S.P.* units per cubic centimeter) and the infrequency of injections required for maintenance (15 or 30 *U.S.P.* units at intervals of two weeks or a month) render the use of any oral preparation a doubtful policy, from the point of view of both effectiveness of treatment and convenience or expense to the patient. Few patients conscientiously persist in taking considerable amounts of medicine by mouth two or three times a day for long periods after they consider themselves perfectly well. Because a definite but unpredictable num-

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ber of patients in severe relapse fail more or less completely to respond to products administered orally in usual amounts, it is certainly unwise to initiate treatment by any other method than that of parenteral therapy, usually in terms of multiple *U.S.P.* units daily for the first few days. A similar indication is provided by patients with pronounced neural manifestations. With exceedingly rare exceptions, the present purified and concentrated preparations seem to be as effective as the older and cruder products in the treatment of pernicious anemia and its neural complications. A practical point in the early detection of the onset of remission is to determine the reticulocyte percentage on the fifth and seventh days after therapy with liver or stomach preparations has been instituted. In the response of anemic patients, the increase of the reticulocytes is so much more striking than the change in red-blood-cell or hemoglobin values in the first week that, relying only on the latter, the physician may fail to realize that the response has already begun.

Although liver extracts, especially the less highly purified products, are to some extent sources of various members of the vitamin B complex, these are apparently unessential to the remission induced by the active hematopoietic principles of liver. The treatment of pernicious anemia by vitamins is thus a waste of material. Whereas it is true that large amounts of whole or autolysed yeast may, under experimental conditions, cause detectable improvement in pernicious anemia, it is probable that these agents act only indirectly through their power to induce the formation of liver extract in the body. In actual practice, they are without significant value compared to the efficiency of active liver or stomach preparations, and their use is an additional burden on the patient and his pocketbook. Whether or not vitamin C is an effective agent in the rare macrocytic anemia of scurvy remains to be proved. Since fruit juice containing vitamin C has been shown to be capable of causing blood regeneration in such patients, it can be readily employed in any case whether its activity depends on ascorbic acid or other factors. Today, the sole essential for maintaining continued and complete remission in pernicious anemia is the exhibition of sufficient amounts of active material by a single route at regular intervals. The advances of the last fifteen years have almost deprived the adjective "pernicious" of any real meaning. Indeed, it is a puzzling question whether the diagnosis "pernicious anemia" should appear on the death certificate of a patient who by adequate treatment has been maintained through many years with a normal blood count and who has died of causes entirely unrelated to his original anemia.

The effective use of iron in the treatment of anemias now known to be hypochromic is older than the record of history. Its latest and presumably permanent reappearance on the platform of sound therapy dates from the independent observations of Barkan and Meulengracht, in 1923, in Europe. They abandoned the small amounts of iron advised by theory and used dosages comparable to those effectively employed today. It is now known that almost any sort of iron, if orally administered in a finely divided form or as a nonirritating iron salt, is effective in the treatment of hypochromic anemias in which loss of hemoglobin and consequently of iron has been brought about by bleeding, pregnancy or growth. Observation shows that ferrous compounds are in general more effective than ferric. The dosage of ferrous compounds is about 5 gr. three times a day, best given just after meals to avoid gastric irritation. Many injections of iron have been made without much effect because of the minute amount of iron in these often expensive and elegant ampules. Today, it is recognized that it is very rarely necessary to promote hemoglobin regeneration by injections of iron. If, however, because of failure of oral therapy in adequate dosage, such a procedure is required, suitable preparations — sterile solutions of ferric ammonium citrate or ferrous gluconate — are available.

The indication for the use of iron is a low hemoglobin concentration in the red blood cells or a low color index. Unfortunately, the hypochromic anemia of chronic infections and that of the so-called "Mediterranean anemia," although possessing these characteristics, do not respond to iron. Experimental animals with hypochromic anemia that have failed to respond to iron are often relieved by vitamin B_6, but this is not true of patients, at least in my experience. In growing experimental animals, carefully deprived of access to copper, it has been convincingly shown that this element as well as iron is essential for relief of the anemia that develops. Some authors have reported a similar use for copper in anemic infants given small doses of iron. There is, however, no convincing evidence that patients failing to respond to usual doses of iron will respond to the addition of copper. Liver and stomach preparations are useless. Moreover, undiscriminating polypharmacy obscures the effective agent and may lead to needless and expensive types of maintenance therapy. Iron, therefore, appears to be the only agent of practical importance in the treatment of hypochromic anemia.

Patients with myxedema commonly have some degree of hypochromic and occasionally macrocytic anemia, especially if gastric anacidity is pres-

ent. Hypopituitary syndromes are also sometimes associated with anemia. Treatment in both conditions depends on suitable endocrine therapy, and may be accelerated by the use of liver extract or iron, according to the character of the anemia.

Chemotherapy

Chemotherapy, although primarily employed for the infection itself, is more than incidentally a means of combating hemolytic anemias, such as those due to the streptococcus or to the malaria parasite. The unrecorded experiments of Indians with Peruvian bark long antedate modern chemotherapy. The latest advance is that initiated by Domagk in 1933 by the discovery of the bacteriostatic action of a sulfonamide in experimental streptococcal infections. To discuss in detail the use of sulfonamides or quinine is obviously beyond the scope of these remarks. Chemotherapy may also be of value as an accessory in the treatment of blood dyscrasias of which an infection is an important complication. Thus, the advent of an infection of the respiratory or urinary tract may even be fatal in a patient with severe anemia otherwise easily amenable to therapy. The signs of infection, however, may be falsely simulated in a patient with a hemoglobin level of less than 25 per cent by a fever of 1 or 2°F. that may be entirely due to the anemia; even higher temperatures may result when an active hemolytic process is present entirely without infection. For the local-tissue necrosis and secondary infection encountered, usually in the oral cavity, in agranulocytosis, aplastic anemia or leukemia, especially the monocytic variety, the relatively small experience available already indicates a value for the sulfonamides. Their utility consists in holding in check the invasion of the infection until other remedies may have an opportunity to act on the underlying blood dyscrasia.

It seems clear that in general, as in the presence of primary infections associated with leukopenia, the possibility of further depression of the granulocytes is not so great a risk as the danger from the infection when uncontrolled by chemotherapy. Sulfonamides, like certain other cyclic compounds, have caused acute hemolytic anemia, leukopenia, thrombopenic purpura and aplastic anemia. Fortunately, such undesirable results occur in only a very small percentage of cases, and their manifestations can usually be prevented by early detection. Because the chance of such an occurrence is small, one should never hesitate to administer these valuable drugs when a serious infection presents a clear indication for their use. On the other hand, the widespread and indiscriminate employment of the sulfonamides for trivial infections may well produce from only a small percentage incidence a considerable number of hematologic complications, immediate or remote.

Splenectomy

In 1911, Micheli observed the benefit of splenectomy in a case of acquired hemolytic jaundice, and in the next two years, Eppinger and Banti independently reached the conclusion that it was a logical and successful procedure in congenital hemolytic jaundice. In this community, Dameshek has recently done a service by calling attention to various types of acquired hemolytic jaundice and by re-emphasizing the therapeutic value of splenectomy in some of them. The success of splenectomy in such anemias depends on the predominance of pathologic blood destruction in the spleen. In congenital hemolytic jaundice, the red blood cells almost invariably exhibit some increase in fragility in hypotonic saline solution, and the spleen is usually large and the pulp engorged with blood. A successful splenectomy is almost always dramatically effective in returning the patient's blood values to normal. If necessary, as a preliminary to operation, rapidly repeated transfusions should be given to bring the hemoglobin level to at least 50 per cent of normal. Although this may be difficult in the face of a crisis of rapid blood destruction, splenectomy not only promptly abolishes this phenomenon but also, by extrusion of blood from the spleen during operative manipulation, provides an autotransfusion, often immediately raising the hemoglobin level by 15 per cent or more. Consequently, splenectomy should not be unduly delayed.

In patients with acquired hemolytic jaundice, a term that includes several distinguishable acute and chronic forms of disease, a generalization concerning the effect of splenectomy is impossible. Perhaps, however, it can be stated that after certain causes of hemolytic anemia that are amenable to other forms of treatment have been excluded, splenectomy is likely to be beneficial if the fragility of the red blood cells in hypotonic saline solution is significantly increased and if the spleen is distinctly enlarged. Splenomegaly alone, however, provides no guarantee of success for splenectomy. Before the procedure is undertaken, the duration and nature of the hemolytic process should be carefully studied. Thus, in acute cases, the history may reveal exposure to hemolytic compounds, such as phenylhydrazine, sulfanilamide and arsine, or in other cases, dark urine (hemoglobinuria) after exposure to cold or after sleep. A blood culture or film may demonstrate septicemia due to bacteria or malaria parasites. Exposure to pure carbon dioxide causes anoxic microscopic sickling in sickle-cell anemia, and in paroxysmal nocturnal hemoglobinuria alone, the carbonic acid causes

hemolysis. A positive serologic test for syphilis and hemolysis on chilling (Donath–Landsteiner phenomenon) confirm the diagnosis of paroxysmal hemoglobinuria *e frigore*. Such patients are not suitable for splenectomy. In other patients, autoagglutination of the red blood cells has been remarked; Dameshek has found hemolysins in the serum independent of isohemolysins in a certain group of cases. Bone-marrow biopsy or splenic puncture may disclose other causes of acquired hemolytic anemia, such as aleukemic leukemia, Hodgkin's disease and agnogenic myeloid metaplasia. Suffice it to say that if the conditions enumerated above, which are amenable to other types of therapy, can be excluded and if severe hemolytic anemia with acholuric jaundice and manifest signs of active blood regeneration persist for some days despite frequent transfusions, splenectomy may be indicated, at least as a means of somewhat reducing excessive blood destruction and, possibly, of abolishing it.

It is to be emphasized that the expectation of success from splenectomy in so-called "acquired hemolytic jaundice" is quite different from that in the congenital condition, and as in thrombopenic purpura, although splenectomy is the only therapy likely to be effective, its success is far from certain. Likewise, splenectomy in Banti's syndrome, in which the hypochromic anemia is probably to a considerable extent due to chronic and often occult bleeding from varices, is not always of benefit. The operation is often technically difficult because of the adherence of the spleen to nearby structures, and only when the obstructing vascular lesion is confined to the splenic vein is there considerable certainty of complete relief. Unfortunately, some type of hepatic cirrhosis is most frequently responsible for "chronic congestive splenomegaly," the highly appropriate descriptive term for Banti's syndrome that was coined several years ago by a Boston physician, the late Dr. Ralph C. Larrabee.

Irradiation

Irradiation by roentgen rays or radioactive phosphorus is today considered the chief weapon in treating leukemias and related conditions. Yet, although in discussions of such treatment great attention is paid to the number and character of the leukocytes, a disabling and frequently fatality-determining feature of leukemia is the anemia that sooner or later appears. Indeed, the problem in the irradiation of leukemias is not so much how to effect a reduction in the number of white blood cells as how to increase the number of red blood cells (or platelets). Since it is usually considered unsafe to apply x-ray therapy in the presence of severe anemia, preliminary transfusions to bring the hemoglobin to a level of at least half the normal value are indicated.

The justification for discussing the use of irradiation, a highly technical procedure requiring special apparatus and experience, is that the best results from such therapy in leukemias can be obtained only when collaboration between clinician and roentgenologist is close and intelligent. It is assumed, for purposes of discussion, that the anemia in the leukemias is due to a considerable extent to the mechanical inhibition of normal red-cell production in the marrow cavity by overcrowding with immature leukocytes. In other cases of myelophthisic disease, the bone marrow is invaded by the cells of metastatic carcinoma or is replaced by lipoid-bearing cells or by fibrous or osseous tissue, as in osteosclerotic anemia. Because the cells of most metastatic carcinomas, like those of fibrous or osseous tissue, are presumably insensitive to irradiation, no improvement of the red-cell level is to be expected from irradiation in such cases. Accordingly, when there is doubt regarding the character of the disturbance in the marrow, sternal biopsy is indicated before one decides whether x-ray therapy is to be given.

Although the use of x-rays in the treatment of leukemia was introduced by Senn as early as 1903, it is even now difficult to choose the most suitable procedure and amount among the variety of methods and dosages that have been and still are employed. Experience agrees, however, that in acute leukemias the process is inherently of such a kind or its rate of progress is so rapid that irradiation is not only useless but detrimental. By contrast, in the management of chronic leukemias, especially the myelogenous, the skillful use of irradiation is frequently a means of providing a comfortable and useful existence during months or even years.

In the treatment of chronic leukemias, a trend can be observed toward the use of small amounts of irradiation applied to the body generally, in contrast to heavy local exposure of obviously enlarged organs, such as the liver and spleen. Because the abnormal cells in chronic leukemia diffusely invade the active bone marrow, this tendency seems logical. Since, however, it is never possible to gauge with accuracy the effect of a physical agent on a complex biologic system, overdosage of the entire bone marrow is most surely avoided by exposure of only a portion of it to the action of x-rays at one time. It is desirable, whenever possible, to avoid heavy local irradiation, which, despite a selective effect on immature cells, injures all cells — even those of normal tissues. I have observed enlargement of the spleen to remain substantially undiminished after relatively

large doses of x-ray therapy applied locally, only to have the organ later diminish in size, apparently as a result of repeatedly administered small amounts of general irradiation. If an interval at first of a few days and later a week or two is allowed to elapse between exposures of a quadrant of the body to no more than 75 to 100 r, a leukocyte count preceding each contemplated irradiation becomes a good measure of the effects of previous therapy and thus tends to prevent overdosage. Finally, observation suggests that significant increase of red blood cells may not begin for some weeks after sufficient irradiation to cause marked lowering of the leukocyte count. Because it is seemingly within the somewhat narrow range of dosage between suppression of leukocyte production in the marrow and suppression of erythrocyte production that the effects of irradiation are most beneficial, it is desirable to proceed with sufficient deliberation to allow for observations on the production of both types of cells.

The use of radioactive phosphorus, logically introduced in the treatment of leukemias by Dr. John H. Lawrence, of San Francisco, is still undergoing evaluation. Nevertheless, it seems probable from the results already reported from several localities that radioactive phosphorus is not the final answer to the problem. The impression gained by one who, it should be said, has had no personal experience with the method is that it represents, like x-ray therapy, a form of irradiation theoretically more selective in its effects on leukemic cells and simple to administer. To my mind, however, it has the theoretical objection that all the hematopoietic organs are exposed simultaneously to irradiation. Nevertheless, eminently satisfactory results have been obtained with radioactive phosphorus in the treatment of chronic leukemias, especially those classified as myelogenous. It is still too early to be certain that such effects are superior to those obtained with modern x-ray treatment. In the management of acute leukemias, aleukemic leukemias and leukemias in which severe anemia persists with or without previous x-ray treatment, radioactive phosphorus appears to fail to cause benefit as consistently as any other form of irradiation does.

Transfusion

The final therapeutic aid in the treatment of anemia is blood transfusion. Today, the use of citrated blood, possessing as it does the important advantages of comparative leisure in collection and administration and convenience in transportation or storage, is the method of election. In spite of theoretical objections, fresh citrated blood apparently possesses no practical disadvantages compared with unaltered whole blood. Increased care in the preparation of glassware, tubing and citrate solutions has eliminated many of the febrile reactions to such transfusions. Since, with anemia, the hemoglobin content of the recipient's blood is always reduced, whole blood rather than fresh, preserved or reconstituted plasma is the medium of choice. Thus, in the treatment of anemias, the plasma serves largely as a vehicle for the conveyance of red blood cells. Were it possible at present—when war places a premium on the collection of plasma—to discover a means of preserving the discarded red blood cells intact over relatively long periods, this by-product of emergency activity would no longer largely be wasted.

In the treatment of anemia, blood transfusion plays a significant, although entirely passive, role. Since the hemoglobin concentration in the circulating blood is increased, the blood is better able to carry oxygen from the lungs to the body tissues. With one unimportant exception, there is no evidence that transfusion has a stimulating action on the bone marrow, so far as the production of red or white cells or platelets is concerned. The exception is that, as a result of the eventual destruction of the transfused red blood cells, iron and possibly other materials necessary for new red-cell production may slowly be made available. This delayed and feeble action of transfusion, demonstrable only in hypochromic anemia, can scarcely compare with the effectiveness of the oral administration of a few grams of iron. On the other hand, there is no evidence that transfusion has any depressing effect on the bone marrow unless it raises the hemoglobin above normal values. Transfusion never passively raises the recipient's leukocyte count for more than a few minutes, but may, probably by introducing platelets, cause a cessation of bleeding in thrombopenic purpura for several hours or a few days. The effect of transfusion on bleeding in hemophilia is by virtue of the introduction of a clot-accelerating agent, probably enzymic, associated with the plasma globulins.

Transfusion provides a valuable and sometimes lifesaving procedure in the treatment of anemia, for it may give time for other methods of treatment to become effective or for spontaneous improvement to occur. Thus, patients with sufficiently low hemoglobin values may die before the effect of liver extract or iron therapy takes place. The use of transfusions as a means of carrying patients through hemolytic crises or of preparing them for splenectomy or for x-ray therapy has already been mentioned. In patients with a temporary suppression of red-cell production, as in benzol poisoning, adequate hemoglobin levels may be artificially maintained until Nature initiates new blood formation in the bone marrow. Finally, in patients with aplastic anemia, or with aleukemic

leukemia, a reasonably comfortable existence may sometimes be prolonged for many months by the skillful use of transfusions alone.

For the effective employment of transfusions, two conditions must be met: blood must be readily available and of the proper type; and the technic of the transfusions must be satisfactory and their use judicious. The availability of suitable blood in urban communities is largely an economic question. In fact, the cost of repeated transfusions often becomes prohibitive for many persons able to employ private physicians. The relative difficulty of drawing blood in the past and the comparative rarity and dramatic setting of the procedure have much to do with the present high cost of a pint of blood in many localities. Rarely, today, does the professional donor from whom blood was formerly drawn by an incisional approach to his veins have this unnecessary cause to raise the value of his contribution. The solution, like that of other price situations depending on the economics of supply and demand, will probably come through extension of the organization and invention that have produced the blood bank, the volunteer-donor registry and the emergency blood-procurement service. It is logical to replace the iron lost by the donor by means of a two weeks' course of orally administered ferrous iron.

Time does not permit a discussion of the problems of blood typing except to say that mistakes can most certainly be avoided by the use of typing serums of high agglutinating titers. The relatively rare possibility of the development of anti-Rh agglutinins by the recipient during pregnancy or as a result of previous transfusions has recently been disclosed by the brilliant work of Landsteiner, Wiener, Levine and their associates. A final direct test involving incubation of the donor's cells in the recipient's serum for half an hour, with subsequent microscopic inspection, will almost certainly detect incompatibilities, although to determine their precise nature may require special methods. However, despite the use of compatible blood and of scrupulous care, some unknown quality of certain patients with anemia due to other causes than blood loss renders mild or even severe febrile reactions likely to occur.

From the recipient's point of view, the technic of transfusion includes skillful venipuncture with a short-bevel needle of small caliber that tends to minimize injury to the vein. The blood should be run in slowly, especially in severely anemic patients, to avoid a sudden increase in blood volume, which may overburden an already hard-pressed circulation. The alkalinization of the recipient's urine with 12 gm. of sodium bicarbonate, given an hour or two before transfusion, prevents the precipitation of hemoglobin in the renal tubules if, for any reason, hemoglobinuria results from the transfusion. As a "biologic test," it is desirable to inject not more than 50 cc. of blood in the first half-hour and to watch for symptoms and signs of a reaction. In the management of patients with anemia, the fact that subsequent transfusions may be required should always be borne in mind. Although cutting down on the recipient's vein and its ligation after transfusion are rarely necessary, this unfortunate practice still exists. As a result, patients whose veins have been destroyed by several previous transfusions may present a serious technical problem. Fortunately, in such cases, it is sometimes possible to use the femoral vein or, according to the recent work of Tocantins, to infuse blood directly into the marrow cavity of the sternum. Aside from its physiologic benefit to the patient, the facile performance of transfusion has a desirable psychologic effect in dispelling the dramatic or ominous connotations of the method in the mind of the layman.

If the use of transfusions is to be fully effective, the objective to be obtained should be kept clearly in mind. For example, if the hemoglobin level of a patient with pernicious anemia is considered dangerously low for the interval of a few days before parenteral liver-extract therapy becomes effective, a single transfusion often suffices. On the other hand, in a patient with a type of anemia in which improvement may be long delayed or may never occur, transfusions repeated at appropriate intervals should be given to raise the hemoglobin and to maintain it at a level compatible with moderate activity in convalescence or at light work. It is a waste of precious and potentially useful weeks or months of such a patient's life if, owing to parsimony in the number of transfusions, he is needlessly confined to bed or home.

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It is a truism that proper treatment depends on accurate diagnosis of the type of anemia. Perhaps it is not so well known that this is often impossible from the examination of the blood alone but requires, as in any other field of medicine, careful history taking and physical examination and special laboratory examinations. The final proof of the correct diagnosis of nutritional-deficiency anemias is an orderly hematopoietic response to substitution therapy at the expected time. Because certain types of anemia may masquerade as cardiac, renal, nervous or even orthopedic conditions, a correct determination of the patient's hemoglobin level should be as routine a procedure as the performance of a urinary examination. Even when one is dealing with an incurable ailment, therapy effectively directed at an associated anemia may sometimes bring reward to both patient and physician.

FAMILIAL NONHEMOLYTIC JAUNDICE*

Report of a Case with Liver Biopsy

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UNDER the designation "familial nonhemolytic jaundice," Dameshek and Singer[1] recently reported a group of cases of mild acholuric jaundice occurring in several members of two families. Although congenital hemolytic jaundice was at first suspected in these cases because the van den Bergh reaction in the blood was "indirect" and the urine contained no bile, this diagnosis was conclusively ruled out because none of the evidences of increased blood destruction (spherocytosis, increased hypotonic fragility, increased fecal urobilinogen output and so forth) were present, and there was no evidence of increased activity on the part of the bone marrow (polychromatophilia, reticulocytosis, high platelet count and so forth). On the other hand, organic hepatic disease seemed unlikely in view of the lack of progression of jaundice over a period of years and because the various tests for liver function were negative. That the condition was due to a specific functional disturbance in the excretion of indirect bilirubin from the blood by hepatic cells was indicated by the bilirubin-excretion test, which invariably showed a marked retention of injected bilirubin. It was believed by these authors that the liver itself was organically normal, especially since Malloy and Lowenstein[2] had discovered families of jaundiced rats with an identical picture in which histologic studies of the livers were uniformly negative. Although Dameshek and Singer were unable to perform biopsies of the liver in their cases, Krarup and Roholm[3] recently reported 5 cases of a similar or identical condition ("icterus intermittens juvenilis"[4]) in which aspiration biopsies of the liver were negative. In none of the previous cases[5] were biopsies of the liver reported. In the present investigation, there was opportunity for a detailed study of a patient with the typical features of the familial nonhemolytic condition; biopsy of the liver was performed at operation. In addition, it was possible to study sections of the spleen, which had been removed several years previously under the impression that the case was one of familial hemolytic jaundice. The results of these studies, which showed a normal histology of both the liver and spleen, are the subject of the present report. The lack of response to splenectomy again indicates the necessity for differentiating the disorder from hemolytic jaundice.

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CASE REPORT

P. M., a 50-year-old divorced Irishman, was admitted to the Third (Tufts) Medical Service of the Boston City Hospital on May 25, 1941, in a state of marked disorientation, possibly alcoholic.

Physical examination revealed a well-developed and well-nourished man with marked jaundice of the skin and scleras. There was no abdominal tenderness or spasm, the liver was not palpable, and there was a well-healed longitudinal incision in the left upper quadrant. There were no abnormal neurologic signs, and the remainder of the physical examination revealed no significant abnormalities.

Under symptomatic treatment, the state of mental confusion cleared completely in 2 days, at which time the following history was elicited.

The patient and an older sister had been yellow since birth. The parents and three other siblings had never been jaundiced. A paternal cousin was jaundiced at birth, but the icterus soon disappeared. The patient had two children, neither of whom had ever been jaundiced, and there was no other history of jaundice in the family.

Because of their yellow color the patient and his sister shunned all social contacts, and were frequently ridiculed as "Chinks" by neighbors and even by members of their own family. This resulted in the formation of a close emotional attachment. As children, both developed normally. Neither had ever had pruritus or undue fatigue, nor had they noticed dark urine or clay-colored stools. They had never shown any gastrointestinal symptoms, and the jaundice, although varying somewhat in intensity from time to time, had never been related to food intake. Since the age of 18, the patient had been a "moderate" whiskey drinker; bouts of drinking seemed to increase his jaundice.

The first admission, in May, 1918, was at another hospital, where the patient was admitted for study of his jaundice. The notation was then made that he had contracted syphilis 5 years previously, and had received oral mercurial therapy for 6 months. Positive physical findings at that time were: icteric skin and scleras, splenomegaly (?) to 2 cm. below the left costal margin, and the presence of a penile scar. The blood Hinton reaction was positive. The laboratory data are presented in Table 1. The diagnoses were hereditary jaundice and syphilis. The patient was discharged to the Outpatient Department, but failed to attend.

He was next seen in August, 1923, at the Boston City Hospital, this time because of "nervousness." Physical examination, except for jaundice, was entirely negative. The laboratory data are shown in Table 1. A diagnosis of hereditary jaundice was also made.

The patient was readmitted in September, bleeding profusely from self-inflicted slashes of the wrists and neck. He revealed that he had "double-crossed" his jaundiced sister in a real estate transaction and, in a state of marked depression, had attempted suicide. Physical examination revealed lacerations of the neck from ear to ear, and several smaller lacerations of both wrists. Except for jaundice, no physical abnormalities were noted. On entry, the patient presented a picture of marked hypochromic anemia due to blood loss. Extensive laboratory studies were performed (Table 1). A diagnosis of atypical familial acholuric jaundice was made, and splenectomy was recommended.

On November 19, when the blood had returned to normal, splenectomy was performed. At operation, the spleen was found to be normal in size and consistence. The jaundice became somewhat less intense following operation.

During convalescence, the patient developed auditory hallucinations and was committed to the Boston State Hospital, where he remained for 14 years as a case of manic-depressive psychosis, depressed state, and where his stay was uneventful.

After discharge, he was employed as a restaurant worker, and enjoyed good health until admission to the Boston City Hospital.

Examination of the blood showed a red-cell count of 5,020,000 with a hemoglobin of 14 gm. (90 per cent), and a white-cell count of 13,900 with 1,900,000 platelets and 1.2 per cent reticulocytes. The hematocrit was 47 per cent, the mean corpuscular volume was 94 cu. microns, the mean cell diameter was 8 and the mean cell thickness was 1.87 microns. The blood smear showed 54 per cent polymorphonuclears, 34 per cent lymphocytes, 3 per cent monocytes, 7 per cent eosinophils and 2 per cent basophils, with occasional target cells and Howell–Jolly bodies. Rouleaux formation was normal. The red-cell fragility to hypotonic saline solutions began at 0.44 and was complete at 0.12 per cent. An aspiration biopsy of the sternal marrow was negative.

Numerous urinalyses revealed no bile or increase in urobilinogen content. The serum bilirubin ranged from 3.4 to 12.6 mg. per 100 cc. in fasting blood samples, and always gave the indirect van den Bergh reaction. The total serum protein was 5.6 gm. per 100 cc., with 3.8 gm. albumin and 1.8 gm. globulin. The blood cholesterol was 240 mg. per 100 cc., with esters accounting for 180 mg. The bile acids (Thannhauser and Ginsburg[6]) were 2 mg. per 100 cc. The blood Hinton reaction was positive.

Liver-function tests showed no bromsulfalein retention after 15 minutes. Another determination showed 20 per cent retention in 15 minutes. The hippuric acid excretion was 3 gm. Bilirubin-excretion tests were performed on three occasions, but the results, although indicating marked retention, proved unsatisfactory, owing to the unusually high fasting serum-bilirubin level. The prothrombin time was normal. The daily fecal urobilinogen output ranged from 8 to 25 mg. (normal 50 to 200 mg. per day). This was unaltered by the daily administration of 1.2 gm. of sodium dehydrocholate (Decholin) intravenously.

On x-ray examination, the patient's chest and skull showed no abnormality. The gall bladder failed to visualize after oral cholecystography. Intravenous cholecystograms revealed a normally functioning gall bladder. A gastrointestinal series showed a chronic duodenal ulcer, and a barium enema revealed a diverticulum of the sigmoid.

Exploratory laparotomy was performed on August 26, under spinal anesthesia. At operation, the liver was normal in size and consistence. The gall bladder was normal in size, color and thickness of wall, and emptied easily on normal pressure. There were many adhesions between the omentum and the site of splenectomy. A small piece of liver tissue was removed.

Histologic examination of sections of the liver was reported as follows:

> The architecture is well preserved. There is a clearly recognizable capsule, and the portal areas, central veins and lobules stand out distinctly. About one third of the portal areas have a slight increase in fibrous tissue and show a moderate lymphocytic infiltration. The smaller branches of the portal vein, the hepatic artery and the smaller tributaries of the biliary system show no evidence of disease. There is no bile stasis, and no dilatation of the bile ducts or bile canaliculi.
>
> The liver cells are well preserved, vary in glycogen content, and contain no recognizable fat. The cytoplasm is granular. There are no giant or necrotic cells. There are no mitoses, and no cells contain alcoholic hyalin.
>
> Pigment is present in the liver cells. There is a very little powdery brownish-green pigment in the liver cells adjacent to the central veins; this does not stain for iron. There is a little iron-containing pigment concentrated about the bile canaliculi in isolated nests of liver cells. There is a third pigment, which is also brown to greenish brown in many liver cells; this is not iron

TABLE 1. *Summary of Significant Laboratory Data.*

DATE	RED-CELL COUNT	HEMOGLOBIN	WHITE-CELL COUNT	HEMATOCRIT	RETICULOCYTES	RED-CELL FRAGILITY	SERUM BILIRUBIN	VAN DEN BERGH REACTION	SEROLOGIC TEST FOR SYPHILIS
	$\times 10^6$	%	$\times 10^3$	%	%	% NaCl	mg./100 cc.		
1918	7.44	80	8.4						++
	6.96	127	11.6						
1923									
Before splenectomy	2.65	50	4.60		2.0	0.46–0.32	10.0	Delayed direct	0
	3.38	55	6.20		1.6	0.40–0.28	6.7		
	2.70	50			2.0		9.0		
	4.25	63					10.0		
	5.10	90							
After splenectomy	4.78	72	14.50	48.0	0.2		2.3	Delayed direct	0
	5.42	90	8.00						
1941	4.55	98	16.15	45.5	0.0		3.4	Indirect	+++
	4.80	95			0.0		6.6		
	4.11	91	9.04	42.0	1.0		9.2		
	5.02	96	11.50	47.0	1.2		4.5		
	5.02	90	13.90	47.0	1.2	0.44–0.12	10.4		
						0.48–0.12	12.6		

staining (it is not like the pigment of bile stasis). There is no demonstrable hemofuscin.

The endothelial cells are present, free of pigment and inconspicuous.

There is no edema, and no thrombosis or hemorrhage.

The sections of the spleen removed in 1923 were also reviewed. The result of microscopic study was: "The spleen shows reticulum-cell and endothelial-cell hyperplasia, leukocytosis, eosinophilia and moderate hemosiderosis."

Laboratory studies performed on the patient's sister showed a red-cell count of 3,940,000 with 76 per cent hemoglobin, and a white-cell count of 7250; the serum proteins were 7.5 gm. per 100 cc., the albumin being 5.2 gm. and the globulin 2.3 gm. The red-cell fragility to hypotonic saline solution began at 0.40 and was complete at 0.32 per cent. The serum bilirubin was 11.9 mg. per 100 cc., and the van den Bergh reaction was indirect. The blood Hinton reaction was negative.

Discussion

All the characteristic features of familial nonhemolytic jaundice were present in this patient.

The familial nature of the disease was established by study of the patient's fifty-four-year-old sister, who had been jaundiced since birth. She was in perfect health, had no complaints and gave no history of alcoholism. Although she was markedly icteric, there was neither hepatomegaly nor splenomegaly. Laboratory data revealed no anemia and a hyperbilirubinemia of the indirect variety. The blood Hinton reaction was negative.

The nonhemolytic nature of the jaundice was revealed by the absence of anemia, reticulocytosis and bone-marrow hyperplasia, the low fecal urobilinogen and the normal urinary urobilinogen values and, finally, the failure of the patient's condition to respond to splenectomy. In addition, the spleen was grossly and microscopically normal.

The absence of organic liver disease was confirmed by the findings at laparotomy. The liver was grossly normal, and the biliary system intact; microscopic examination of a liver biopsy specimen was within normal limits. Alcoholic and syphilitic liver disease were thus ruled out. Numerous tests of liver function — hippuric acid synthesis, bromsulfalein excretion, cholesterol partition and prothrombin concentration — were within normal limits. Bilirubin-excretion tests, although difficult to interpret because of the high fasting levels of bilirubin in the blood, showed a definite tendency toward abnormal retention. It is significant that although a high level of indirect bilirubin was present in the blood, there was a low output of urobilinogen in the feces; this indicated, without further testing, bilirubin retention.

This case is of further interest because it afforded the opportunity of studying the hematologic changes eighteen years after splenectomy. These changes have recently been emphasized by Singer, Miller and Dameshek[7] and are well brought out in the case presented. Thus, there was leukocytosis, with lymphocytosis, occasional target cells and Howell–Jolly bodies, increased platelets, increased hypotonic resistance of the red cells and decreased output of urobilinogen in the feces. The excessively low values for fecal urobilinogen were probably due to the summation of the two factors of delayed bilirubin excretion and splenectomy.

In an attempt to increase the bilirubin excretion, sodium dehydrocholate (Decholin) was injected intravenously on two occasions. In the first experiment, 0.6 gm. was injected twice daily for four days, and the stools were collected during this period. In the second, 4.0 gm. was injected in one dose, and stools were collected for the subsequent four days. On neither occasion was there any increase in the fecal urobilinogen. A control patient with normal urobilinogen excretion also failed to show an increase after one injection of 4 gm. of sodium dehydrocholate intravenously.

This patient represents a living example of the necessity for differentiating familial nonhemolytic and familial hemolytic jaundice. Dameshek and Singer[1] have presented detailed data for making this differentiation possible and have stressed the fact that acholuric jaundice and an indirect van den Bergh reaction need not indicate a hemolytic process. In this and other studies, the value of the fecal urobilinogen output for determining the presence or absence, as well as the degree, of increased hemolysis has become increasingly apparent. Splenectomy in the case presented above apparently reduced the degree of bilirubinemia temporarily, probably through its effect on blood destruction. The contrast between the dramatic cessation of jaundice in familial hemolytic jaundice and the results in this case is indeed striking.

The possibility of familial nonhemolytic jaundice should be considered in every case of persistent, relatively mild, nonobstructive jaundice. It is believed that the condition is commoner than the small number of reported cases indicate.

Summary

A case of familial nonhemolytic jaundice, with biopsy of the liver, is presented. Splenectomy performed eighteen years previously for "familial hemolytic jaundice" failed to alter the course of the disease. The hematologic effects of splenectomy were apparent.

The injection of large doses of sodium dehydrocholate failed to increase the fecal urobilinogen excretion.

The importance of differentiating the familial nonhemolytic condition from congenital hemolytic jaundice is emphasized.

Since this paper was written we have studied four additional cases of familial nonhemolytic jaundice, occurring in three families.

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PILI TORTI HEREDITARIA*

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THE name "pili torti" was first applied by Ronchese[1] in 1932 to a rare developmental anomaly of the hair. He reported the case of a seven-year-old girl, born in Rhode Island, of Italian descent, who was the youngest of eight children and was apparently normal in every other respect except that the teeth were poor and slightly notched, with spaces between them; the hairs on the scalp were dull blond, lank and frizzly, with a wild bushy appearance. The hair had never been cut but broke spontaneously on slight injury at various short lengths from the scalp. Ronchese made numerous interesting and fairly thorough studies of the hair roots and of the hair shaft in various mediums, measured the elasticity and strength of the hair, and examined the hair follicles microscopically. He also discussed the meager previous literature on the subject and came to the conclusion that his case was the second reported in the literature, in which the hair was characterized by fragility and sharp twists on its own axis. He proposed the name of "twisted hairs." His report has been quoted elsewhere in the literature.[2]

Ronchese presented the same case at the Atlantic Dermatological Conference, March 22, 1941, in Boston. During the interval, the patient had been treated only with fairly constant applications of lanolin. Her hair had grown out fairly long, and there was a marked improvement in the general appearance. She was able at that time to dress her hair so that it attracted no attention and appeared quite normal to the casual observer. At a subsequent date, the sister, two years younger than the patient, was examined and showed a similar but much milder condition. There were no definite areas of alopecia of the scalp, but the hair showed the same tendency to twisting, and there was a moderate degree of alopecia of the outer two thirds of the eyebrows. This patient did not show any dental hypoplasia.

Although recognizing that Ronchese first called attention to this condition in 1932, Sutton and Sutton[2] call the disease "pili torti (Galewsky)." It may be presumed that Galewsky's name was added because he[3] described a knotted condition, which he called "trichonodosis," in 1906.

In 1924, Ormsby and Mitchell[4] presented a case of so-called "atrophia pilorum monilethrix" in a two-year-old girl who was born without hair and whose scalp remained smooth until the age of fourteen months. Subsequently, the hairs resembled the beaded hairs in monilethrix, but on careful examination this appearance was thought to have been due to a twisting rather than to a beading of the individual hairs. In discussing the case, Foerster[5] stated that the condition resembled monilethrix, but that under the microscope the hairs showed twisting without any break. The same case was presented under the title "atrophia pilorum" by Ormsby and Mitchell[6] in 1925. At that time, there had been a marked improvement in the general appearance, the hairs had grown longer, and the former beaded appearance was less apparent; Dr. Ormsby, in the discussion, stated that he had not been able to prove that there was either twisting or actual beading of the hairs but that there was unquestionably a congenital atrophy.

Danforth,[7] in his studies on hair, mentions the twisting of hairs on their own axes. He apparently considers this a fairly normal phenomenon, varying in its degree in different hairs. The twisting causes a series of half turns so that one side of the hair is alternately toward and away from the observer. The length of the hair involved in the twist ranges from one to several millimeters. The greater distance renders the detection of the twist-

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ing more difficult. When the twists are closely connected, the hair is given a frizzly character. This twisting, which is apparently irreversible and may even be seen within the follicle, is probably determined by the follicle, perhaps by periodic changes in the functions of the papilla. Danforth is of the opinion that this twisting may have an anthropologic significance. Franchi[8] believes that the condition may be due to endocrine damage acting on the sympathetic nervous system.

Hellier et al.[9] described the first case reported from England. They also apparently erroneously credited this name to Galewsky, but Ronchese[10] called attention to his priority in this nomenclature. Hillier and his associates described a two-year-old girl with a fairly typical case, which apparently was at first provisionally diagnosed as monilethrix. An interesting observation that they made points more definitely to a predetermined growth, characteristically residing in the follicle, as the underlying feature producing the twist in the hair. They epilated with thallium acetate by mouth, following which follicular hyperkeratosis was observed; a few months later, when new hair grew in, it still had the characteristic twists. They made x-ray and optical examinations of these hairs and came to the conclusion that the irregularities were not due to any molecular disturbance of the keratin recognizable by x-ray diffraction. The tensile strength of hair in their case showed that the abnormal hairs were about 10 per cent weaker when dry and 25 per cent weaker when wet, which is not too far removed from normal. Moreover, since the authors found that the twisted hairs, when wet, stretched just as far as normal hairs, they conclude that if these hairs were kept damp there would be less risk of premature breaking.

Within the last few years, several other cases have been reported of which Sutton and Sutton[2] present a complete bibliography.

Case Report*

C. F., a 10-year-old girl, was first seen in the Out-Patient Department for Diseases of the Skin at the Boston City Hospital because of an eruption on the face. This was diagnosed as dermatitis venenata, probably caused by a patent mange cure, which had been applied to the scalp by the mother. With usual soothing remedies and the cessation of the use of the preparation, the dermatitis promptly improved.

Figure 1. *Patient's Younger Sister.*
Note that the pili torti hereditaria is relatively slight.

The mother stated that the patient had had a peculiar twisting type of hair since birth. It was somewhat worse when she was younger. Bald areas over the scalp and over the eyebrows were present constantly and were very disturbing. For the preceding 2 months, a large area of relative alopecia over the vertex of the scalp had developed. An older brother and a younger sister of the patient had a similar but definitely less noticeable type of hair; only on careful inspection did the twisting become obvious. The hair of these siblings was softer and could be dressed in a less conspicuous manner, but there was the same tendency toward the thin, straight, frizzled appearance, particularly in the shorter hairs (Fig. 1). The eyebrows were quite thinned out in their outer portions. The younger sister showed no changes in the enamel of her teeth. Her general physical condition was normal. The paternal

*This case was presented at the Atlantic Dermatological Conference, Boston, March 22, 1941.

aunt and grandmother were similarly affected. This was as far back as any cases were known to the parents.

The patient's hair over the entire scalp was dark blond, with a peculiar, dry, brittle feel to the touch. The general appearance was frowsy, and on more careful examination the individual hairs varied considerably in length. The ends had a broken-off and the shafts a definitely beaded appearance, which on closer inspection was produced by a twisting of the shaft. On the vertex, there was a large area of alopecia, approximately 7 to 8 cm. in diameter (Fig. 2). In this area, the hairs were broken off at a distance of about 1 cm. from the scalp. The skin of the scalp itself was smooth and normal in appearance, without evidence of inflammation or infection. The eyebrows were very thin, the outer thirds being almost entirely bald. The eyelashes appeared normal.

FIGURE 2. *Patient with Pili Torti Hereditaria.*

Note the frizzled short beaded hairs, the alopecia of outer eyebrows, the enamel defect of teeth and the alopecia of the scalp.

The skin over the entire body was normal except at the neck, particularly posteriorly, where there was a moderate degree of keratosis pilaris. The teeth were irregular in shape, with somewhat wider interdental spaces than normal and with serrated biting edges. The left upper central incisor showed slight projection of the central portion of the biting edge. All the teeth had a peculiar yellowish appearance of approximately two thirds of their free biting surfaces; on close inspection, this was seen to be due to a hypoplasia of the enamel. General physical examination disclosed no other abnormalities.

Microscopic examination of the hair mounted in canada balsam showed a characteristic ribbonlike twisting around the long axis (Fig. 3). These twists were spaced in fairly regular intervals and were at times narrow and at other times wider. The hairs split easily while being handled for the purpose of microscopic examination. When immersed in 10 per cent solution of potassium hydroxide, they swelled and burst in several areas within a few seconds.

This patient and her younger sister are almost identical with the two children described by Ronchese.[1] In addition, the hypoplasia of the enamel of the teeth in the older girl is another characteristic feature that points to ectodermal dysplasia as a probable underlying cause. Ronchese's observation that a twisting of the hair on its own axis is the pronounced feature is in accord with our observation, and should therefore determine the name of the condition — "pili torti"; we further suggest the addition of the term "hereditaria," because of the obvious hereditary character. There seems to be no good reason for attaching the name "Galewsky" to the diagnosis. Furthermore this practice is undesirable: names may have some historical value but add nothing to the scientific value of nomenclature and are often a confusing factor.

The cause of this condition is not definitely known. It is obviously a developmental anomaly, and if there is any definite relation between the hypoplasia of the enamel of the teeth as seen in our patient and as noted by Ronchese in one of his patients, it may well belong to the general classification of ectodermal dysplasia. If the condition were due to any marked endocrine abnormality, it seems to us that the patients previously observed and described in the literature would have shown some evidence of it. That the condition must be rare is apparent from the very small number of cases reported in the literature, in spite of the fact that many diseases of the scalp are under constant observation by dermatologists everywhere.

From the observations on one of Ronchese's patients, it is also reasonable to assume that, as the patients become older, there is a natural tendency for the hair to become less abnormal in appearance. The application of lanolin is apparently the only effective treatment known at present.

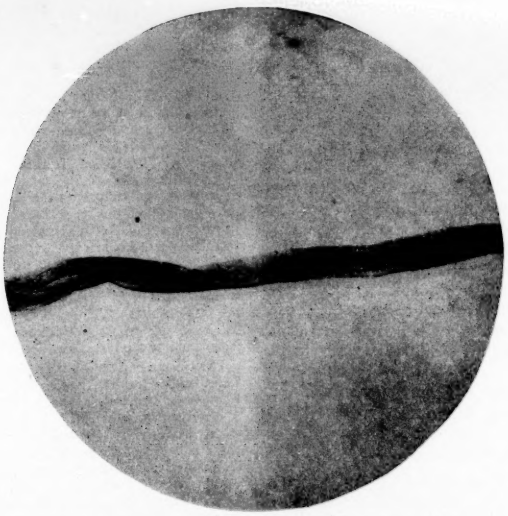

FIGURE 3. *Microscopic Evidence of Twisting and Loosening of Keratin in Strandlike Formation (hair mounted in canada balsam).*

SUMMARY

A case of pili torti hereditaria is presented, and other cases reported in the literature are discussed, particularly from the point of view of etiology, which may well be an ectodermal hypoplasia.

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TYPHUS FEVER IN MASSACHUSETTS*

Report of a Case Contracted in an Out-of-State Endemic Area

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THE comparative rarity of the rickettsial diseases, typhus fever and Rocky Mountain spotted fever, in Massachusetts prompted the report of the following case. Although typhus fever is endemic to the extent of about 3000 cases each year throughout the United States, much of the illness is confined to the South Atlantic and Gulf states.[1, 2] Very few cases have been reported from the New England states, and only 16 cases have been reported in Massachusetts since 1929,[3] including a series of 10 cases observed at the Beth Israel Hospital in Boston between 1929 and 1932 and reported in 1933.[4] Rocky Mountain spotted fever was first reported in the states east of the Mississippi River as early as 1931, and its prevalence since that time has been confined largely to the South Atlantic states.[5] The cases in the United States have numbered almost 500 annually in recent years. Three cases have been reported in Massachusetts since 1938, and 2 additional cases were reported in Rhode Island in 1937.[3, 6]

CASE REPORT

A 55-year-old woman was admitted to the Cooley Dickinson Hospital on March 17, 1941, with the principal complaint of fever, first noted on March 12; the temperature was 103 and 104°F., respectively, on March 15 and 16. This patient, a teacher by occupation, had been known to one of us (J. E. H.) for some years, and the past medical history was entirely negative, except for a cholecystectomy in 1938.

Physical examination on admission revealed very little except the presence of fever and an eruption over the abdomen resembling rose spots. On the 2nd hospital day, this lesion covered the chest, neck and face, and a slight hacking cough appeared. Further extension of the rash was noted on the 3rd and 4th hospital days, with spread to the upper and lower extremities. The eruption was maculopapular and confluent in places, very itchy and dullish red, and at first bore some resemblance to measles. Distinct involvement of the palms and soles was noted. The rash persisted for the next 4 days and slowly disappeared by fading and scaling, complete disappearance being noted on the 10th hospital day. Physical examination of the chest revealed a few rales over the left base, and x-ray evidence pointed to congestion in the same area. The temperature from the time of admission ranged between 102 and 104°F. until slow lysis appeared on the 8th hospital day, or 13 days after the onset of fever. The patient was discharged from the hospital on the 14th day after admission, and recent inquiry indicates complete recovery. Supportive treatment was given as indicated.

Urinalyses on two occasions revealed a trace of albumin. Repeated examinations of the blood showed a slight reduction in the red-cell count during the course of the illness. The white-cell count fluctuated between 4700 on admission and 8700 on discharge. Polymorphonuclears ranged from 51 to 80 per cent, the lymphocytes ranging from 16 to 48 per cent; the relative lymphocytosis was most marked on admission. The blood Hinton reaction was negative. Blood cultures on the 2nd and 6th hospital days were negative. Stool culture on the 3rd hospital day revealed no organisms of the typhoid-paratyphoid group. Agglutination tests for typhoid, paratyphoid and undulant fever and the Weil–Felix reaction were negative on the 2nd hospital day. These tests were repeated on the 4th hospital day, and the Weil–Felix reaction was positive in a dilution of 1:40. The titer of the reaction increased to 1:400 on the 10th hospital day and fell to 1:80 in September. Isolation of the suspected infectious agent by guinea-pig inoculation of the blood was not done.

The assistance of the National Institute of Health, United States Public Health Service, was secured in the differential diagnosis of typhus and Rocky Mountain spotted fever. A blood specimen obtained on the 11th hospital day was reported positive to the Weil–Felix reaction in a dilution of 1:5120. The complement-fixation test for typhus recently developed in that laboratory was applied and gave a positive test in a dilution of 1:128. Additional specimens were submitted the following September and October, and the most recent titer of the Weil–Felix reaction was noted to be 1:80, the complement-fixation test being positive in all dilutions up to and including 1:512.

Further inquiry concerning the recent travels of this patient revealed that she had left Northampton on February 16, in the company of a fellow teacher, for an automobile trip to Florida. They arrived in Florida on February 26, and the patient resided until March 13 at the home of a cousin. Mild weather enabled her to indulge in considerable outdoor activity, including swimming and picnicking. No particular exposure to ticks, fleas or lice was noted. However, a prominent scabbed area resembling an insect bite was noted in the left scapular region at the time of hospital admission, and this was considered an extraordinary finding by the patient and her companion. The end of their visit in Florida came the day after the appearance of the fever on March 12. This did not prevent the patient's return, although she was obliged to seek medical assistance in Washington on March 15 and 16, when examination revealed a few "spots" on the abdomen and a temperature of 104°F. The remainder of the trip was made by train.

Much diagnostic confusion was created by the unusual clinical features of this case, and typhoid fever was the first illness suspected. The first four days in the hospital brought the development of the rash to a point where a virus or rickettsial illness was considered. The sustained fever, along with the unusual distribution of the eruption over the palms, soles and head, caused the

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attending physician (J. E. H.) to suspect Rocky Mountain spotted fever. Subsequent laboratory work confirmed the presence of a rickettsial infection and made the earlier diagnosis of typhoid fever unlikely. Closer study of the epidemiologic features of the rickettsial infections indicated that typhus fever was the more probable diagnosis. The relative rarity of Rocky Mountain spotted fever in the early months of the year and the year-round incidence of typhus fever reinforced this impression. Furthermore, this patient had recently returned from an area of relatively high incidence of typhus fever.

Correspondence with the United States Public Health Service brought further support for the diagnosis of typhus fever. Their assistance was secured in the testing of the serum of this patient by means of the complement-fixation reaction recently developed by Bengston and Topping,[7] of the National Institute of Health. Tests on two occasions were clearly positive. Recent studies from the same source indicate a high degree of specificity for this test.

Since no specific serotherapy was available, only supportive and symptomatic treatment was given this patient. The sulfonamide drugs were not used.

Summary

The details of a recent case of typhus fever in a Massachusetts resident are presented. It is likely that the infection was contracted in an out-of-state endemic area recently visited by the patient.

In the differential diagnosis, a specific complement-fixation test recently developed at the National Institute of Health was utilized. Isolation of the infectious agent by animal inoculation was not attempted.

The recent prevalence of two common rickettsial illnesses, Rocky Mountain spotted fever and typhus, in the United States and in Massachusetts is briefly reviewed.

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MEDICAL PROGRESS

VASCULAR DISORDERS OF THE EXTREMITIES

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BOSTON

Obstructive Arterial Disease of Legs

Clinical Tests for Peripheral Arterial Deficiency

THE usefulness of the simpler tests in confirming or refuting the results of the history and routine physical examination is discussed by Montgomery, Naide and Freeman.[1] In all vascular deficiencies, an estimate of the reduction of the arterial supply and the amount of the collateral circulation should be made. A rough estimate of arterial blood flow is secured by observation of the color of the toes when the legs are elevated to an angle of 30° for a minute or two (rapid paling is unfavorable; persistence of pinkness is favorable) and when they are depressed (delay in appearance of pinkness followed by rubor is unfavorable; rapid appearance and persistence of pinkness is favorable).

In connection with the degree of arterial deficiency, the level at which the arteries are seriously constricted or occluded can be discovered by *oscillometry* and by the *histamine test*. After the state of the peripheral pulses in the feet and legs has been learned, the vigor of the pulse wave at various levels should be observed by the use of the aneroid sphygmomanometer. The cuff being firmly applied somewhere in the calf and blown up to a pressure between diastole and systole, the normal excursion of the needle with each pulse beat will be from 1.5 to 3.0 mm. An excursion of 0.5 mm. or only a trace in one leg, as compared with one of 1 or 2 mm. in the other, indicates that a large vessel is occluded at the level tested or higher. Such an observation is frequently made in thromboangiitis obliterans. When pulsations in both feet are absent, oscillometry may call attention

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to a thrombosis decidedly higher in one leg than the other. The presence of a serious occlusion at some particular level may also be noted by the histamine test. Before the test is made, any overlying functional vasoconstriction should be overcome, as by gently warming the skin (with the hands). One performs the test by placing a drop of a 1:1000 solution of histamine acid phosphate on the dry, clean skin, by needling the skin several times through the drop and by feeling for a wheal. Should a wheal fail to appear in three to five minutes, the tissues are so ischemic that an incision at or below the level tested, as for amputation, is unlikely to heal. The presence or absence of a satisfactory wheal low in the leg has useful prognostic significance when the problem is not one of immediate amputation.

The worth of different vasodilatation tests, that is, of the patient's capacity for vasodilatation in response to various stimuli and to sympathetic paralysis (heating the other extremities, heating the body, administering foreign protein, sympathetic procaine block, spinal anesthesia and so forth) is discussed by Montgomery, Naide and Freeman and by Ochsner and DeBakey.[2] In the presence of organic arterial deficiency, these tests demonstrate the capacity of the remaining arteries for dilatation and, in general, the availability of the collateral circulation. In cases of generalized functional vascular constriction, such as is present in cyanotic, sweaty extremities, the tests recognize this state and predict relief by sympathectomy. (It should be noted that the tests may fail in two respects: they do not foretell the result of sympathectomy in improving, over a long period, the nutrition of the feet in the serious arterial deficiencies of both thromboangiitis obliterans and arteriosclerosis, and they may not relax the most serious gross arteriospasms, such as those that are rarely associated with thrombophlebitis and trauma and are subsequently discussed.)

Procedures for Securing Vasodilatation

Several methods for producing vasodilatation have recently been scrutinized, notably, intermittent venous occlusion and the administration of a number of chemicals. Intermittent venous occlusion, brought up to date through the invention of an automatic apparatus by Collens and Wilensky,[3] appeared capable of calling forth a reactive hyperemia. Observations of de Takats, Hick and Coulter[4] were confirmatory. Recently, Linton et al.[5] have conducted experiments revealing the immediate effects of venous obstruction on the circulation in the dog's leg. Arterial flow was measured by the *Thermostromuhr*, and venous pressures were recorded as well. Venous occlusion (clamping the principal vein) was found to increase arterial flow to the extremity. The effect was slower, but still impressive, when the arterial supply was deficient. The increased arterial flow was found to be greater the nearer the heart the venous block was made. When a pneumatic cuff was used, each increase in tightness was followed by a rise in venous pressure and a corresponding rise in arterial flow until the tightness of the cuff reached the level of systolic pressure. Linton and his associates believe that dilatation of the venous tree primarily reduces peripheral resistance and thus permits an increased inflow from the arterial side. Possibly, arteriovenous shunts are opened. Increased arterial flow during increased venous pressure, rather than reactive hyperemia after release of the constriction, is perhaps the chief effect of intermittent venous occlusion. The research supports the value of the division of the principal vein of a limb when arterial occlusion has occurred.

The vasodilating effect of various drugs has been studied by Abramson et al.[6] They used the venous occlusion plethysmographic method, which measures the total blood flow to a portion of an extremity, and made observations on normal persons and on patients suffering from vascular and mental diseases. Calcium gluconate, Padutin, papaverine, Spasmalgin and thiamine chloride produced a slight increase or none in blood flow to the hand, forearm, leg and foot. Alcohol, stilbestrol and histamine generally increased the flow of blood to the hand only. Intravenous hypertonic saline solution augmented blood flow into the leg in only one third of the trials. This is interesting in view of the report of Silbert et al.[7] that the intravenous injection of 300 cc. of hypertonic (5 per cent) saline solution regularly increases blood flow to the muscles of the calf. The latter observations were recorded by the deep thermocouple rather than by methods measuring the total blood flow. One is left with the impression that increased blood flow, as induced by chemicals, is brief and of little importance.

In this connection, Brown and Allen[8] have devised an apparatus intended to secure prolonged vasodilatation in chronic occlusive arterial disease. Reflex vasodilatation is secured by means of a heating sleeve or boot applied to an extremity other than the one diseased. The authors believe that arteriolar dilatation is the effect chiefly secured.

Use of Tobacco

Although the smoking of tobacco has long been recognized as an aggravating factor and a cause of progressive circulatory deficiency in thromboangiitis obliterans, some recent observations are enlightening. Mulinos and Shulman,[9] in a study of the rate of blood flow in the hand, found that deep inhalations without smoke caused vasocon-

striction; that so-called "denicotinized" cigarettes caused a vasoconstriction like that produced by real tobacco; that the response to smoking varied greatly in different persons and in the same subject from time to time; that the actual vasoconstriction, when induced, lasted only about fifteen minutes; and that heavy smokers showed active vasoconstriction even when a systemic reaction to smoking did not take place. Hiestand et al.[10] observed that an increase in the pulse and basal metabolic rates usually, but not invariably, occurred in habitual smokers after the inhalation of cigarette smoke. All such observations indicate that tobacco smoking *may*, by causing vasoconstriction, unfavorably influence blood vessels, in any part of the body, that are diseased in some degree. In this respect, they are not especially impressive. The vasoconstrictive effect of tobacco is very brief. Moreover, observations of Sprague and Homans[11] indicate that heavy smokers suffering from thromboangiitis obliterans may benefit clinically (decided improvement in locomotion through relief of intermittent claudication) by abstinence from tobacco in the absence of Buerger's exercises or other such vasodilating influences even after preliminary observations of cutaneous temperatures in the toes have shown that inhalation of tobacco smoke causes no vasoconstriction whatsoever; and their observations confirm the general impression that abstinence from tobacco leads to recognizable clinical improvement only after many months.

Tobacco may conceivably affect the blood vessels in ways other than by vasoconstriction. Moyer and Maddock,[12] in reviewing the subject, recall the older observations of Harkavy, Hebald and Silbert[13] and of Sulzberger and Feit.[14] The last found that a high proportion of those suffering from thromboangiitis obliterans reacted positively to intradermal injections of various extracts of tobacco (even when nicotine was removed) and not to nicotine itself. Harkavy et al. made similar observations on tobacco-smoking patients who had Buerger's disease, with the additional finding that other smokers rarely so reacted. Since there is reasonably acceptable proof that those who have never smoked occasionally suffer from thromboangiitis obliterans, the question arises whether tobacco acts directly or whether it may not rather reinforce the patient's sensitivity to another adverse influence, such as the presence of a dermatophytosis.

Significance of Dermatophytosis

Thompson[15] suggests that a number of familiar vascular diseases, — namely, thrombophlebitis, phlegmasia alba dolens, migrating phlebitis, thromboangiitis obliterans and postphlebitic ulcer, — seemingly unrelated, have a common background of "endothelial necrosis, thrombosis and chronic inflammation involving the walls of blood vessels and their adjacent tissues." With these disorders, the dermatophytoses of the feet are invariably* associated. Drawing a comparison with tuberculosis, he shows how allergic reactions to antigens derived from the fungi may well constitute the basis of these various lesions. From patients suffering with Buerger's disease and various leg ulcers, he has cultivated fungi from which he[16] has secured a powerful antigen. This antigen provokes in the skin of the legs of persons with such diseases (and not in persons free from them) vivid cutaneous reactions following the intradermal injection of infinitely small doses. Thompson's observations are, of course, in the experimental stage.

Whether or not this line of investigation will prove fruitful and whether or not smoking aggravates supposed allergic reactions of this sort, there is no doubt that effective treatment of dermatophytosis and onychomycosis, combined with abstinence from smoking, has proved of great value in the treatment of thromboangiitis obliterans and other peripheral vascular diseases.

Intermittent Claudication

With the aid of a mechanical device for studying the ability of the muscles of the calf to contract (Hitzrot, Naide and Landis[17]), Freeman and Montgomery[18] have investigated the effect of sympathetic block and sympathectomy on claudication. They found that when a considerable element of abnormal vasoconstriction was present, as indicated by moist, bluish feet and contracted veins, sympathectomy improved the ability of the muscles to work and increased the walking distance. By selecting their cases of both arteriosclerosis and thromboangiitis obliterans on the basis of a favorable reaction to preliminary sympathetic procaine block, they were able to secure a decided improvement in walking. Undoubtedly, the writers prove their point in respect to a favorable effect in selected cases. But that is not to say that one may not see considerable gradual improvement in locomotion as a result of abstinence from tobacco, scrupulous care of the feet and Buerger's exercises (about which combination the writers say almost nothing). Moreover, observations of Wallace and Smithwick,[19] based on a long series of sympathectomies in serious obliterative vascular disease, show that, even in the absence of a favorable reaction to sympathetic block, sympathectomy

*On a purely clinical basis, yet without proof by the demonstration that pathogenic fungi are present in the skin.

causes, over a considerable period, significant clinical improvement (including locomotion) in a great majority of cases.

Vasoconstrictive and Vasospastic Diseases

In the second edition of their excellent monograph, *The Autonomic Nervous System*, White and Smithwick[20] decline to differentiate classic Raynaud's disease and such allied vasospastic conditions as acrocyanosis. They group together the acute, recurrent vasospasms in the extremities, regarded by most observers as Raynaud's disease, with the continued vasoconstrictions, — in fact, all the sympathetic dysfunctions remediable by sympathectomy. This is not in accordance with the usual practice in this country, the definition of Raynaud's disease being decidedly narrow, and excluding all vasoconstrictions and vasospasms except the recurrent spasms of the digital arteries as a reaction to cold and emotion. In this review, Raynaud's disease, in the sense of a vasospastic disorder causing acute attacks of cyanosis or asphyxia of the fingers (and toes) on a background of reasonable normalcy, will not be considered. Smithwick[21] discusses it fully in a recent review of the sympathetic system.

Acrocyanosis

This vague term may properly be applied to the very common reddish-blue, moist extremity. It is difficult to discern the borderline between a richly pink, moist hand and a cyanotic, wet one. In each, there seems to be an exaggerated vasomotor tone in the smaller blood vessels, presumably the arterioles. Social conditions, occupation and self-consciousness or the lack of it make some acrocyanoses and hyperhidroses pathologic, others not.

White,[22] in a picturesque account, strongly recommends preganglionic sympathectomy for hyperhidrosis, since he found no effective palliative treatment.

Regarding acrocyanosis as it commonly occurs in girls and young women, a condition worse in the feet of some patients and in the hands of others, no new information is at hand. The rubor or cyanosis is made worse by cold. White and Smithwick[20] point out that ultimately, in occasional patients, Raynaud's phenomenon of acute, recurrent vasospasm may be superimposed. The background of exaggerated vasomotor (constrictor) tone seems to be curable only by sympathectomy. Recently, several related varieties of acrocyanosis have received attention: namely, livedo reticularis and pernio or erythrocyanosis frigida.

Livedo Reticularis

This is described as a peripheral arteriolar disease by Barker, Hines and Craig.[23] In their cases, the upper and lower limbs were covered with purplish discolorations having various forms: hence the terms, "livedo racemosa," "livedo annularis" and "cutis marmorata." The disease, an uncommon one, was seen equally often in men and women. The extremities, especially the fingers, toes, hands and feet, were subjectively and objectively cold and sometimes painful. The large vessels and peripheral pulsations were normal.

The livid areas, as these and other writers have observed, are most marked and thickly distributed peripherally, gradually becoming less colored as the trunk is approached. They are very persistent, and any one spot is only momentarily whitened by pressure. Warmth turns them toward red or pink. Even a sympathetic block is powerless to make them disappear. Organic changes — perivascular lymphocytic infiltration and fibrosis — were found by Barker et al. to be present in the arterioles, and in occasional cases, serious gangrene of the toes was noted. No etiologic factor is known. Treatment by sympathectomy is justifiable.

Pernio

Pernio, erythrocyanosis frigida and many similar names have been given to the condition commonly referred to as "chilblain," in which a state of peripheral cyanosis is complicated by purplish, raised indurations that ulcerate. McGovern, Wright and Kruger[24] give a thorough résumé of the literature and an authoritative account of the disorder. As in Bazin's disease (erythema induratum), the ulcerations occur principally in the legs of girls. But here, the girls are well nourished, even fat, whereas the victims of Bazin's disease are ill nourished and supposedly tuberculous. In fact, Bazin's disease is believed to be a tuberculid, whereas pernio presents no characteristic pathology.

The authors describe 10 cases, with full reports and with sections of some of the ulcers. The disease, which predominated in young women, appeared in the early winter and disappeared in the spring. The patches, at first red, soon became elevated, hard, purple and painful. They then broke down in part, forming chronic ulcers. Angiitis of the small vessels beneath the ulcers was noted. Although the lower legs were involved in this group, others have noticed similar lesions in the upper extremities when these parts were exposed and the legs were not.

Treatment with acetyl-betamethylcholine chloride (Mecholyl) by iontophoresis and protection from cold are recommended. No mention is made of sympathectomy, of which others spoke in a discussion of the communication and which has been used with apparent success (Homans[25]).

Frostbite

In connection with pernio, the observations of Leriche and Kunlin[26] on frostbite as a "vasomotor and thrombotic disease" are perhaps appropriate. Following various degrees of frostbite, some digits were found to be edematous and blistered, with raised, loosened nails, while others became gangrenous. Even when edema had disappeared and healing had occurred, painful arterial constriction and even intermittent claudication often remained. Such states were helped by repeated sympathetic procaine block. The authors recommend that the *early* stages of frostbite and chilblain, marked by edema and pain, be treated by sympathetic procaine block. Such treatment, in their hands, rapidly relieved cases in which there was no actual necrosis, and was of benefit to all patients.

Arterial Spasm and Arteritis

Traumatic Arterial Spasm

Gross spasm of a temporary or prolonged sort in response to various stimuli is becoming reasonably well understood. The larger arteries of the limbs are most frequently involved. Foisie[27] has recently discussed this subject and has called attention to Griffiths's[28] work on Volkmann's contracture. As a result of a number of surgical explorations, Griffiths opposes the conception that this crippling results from an acute venous engorgement due to hemorrhage within the muscular aponeurosis. The disorder is commonest after supracondylar fractures at the elbow. Tight bandages and acute flexion have been thought to be aggravating factors. Griffiths holds that weakening or loss of the radial pulse is the earliest evidence that trauma has thrown the brachial artery into spasm. His explorations revealed a local contraction of the brachial artery that transmitted a mere trickle of blood, a finding identical with an earlier observation of Montgomery and Ireland.[29] His best results followed resection of the spastic vessel, but he suggests that, in cases of moderate severity, immobilization and the administration of papaverine may be effective. Stripping the artery has not been successful, nor has sympathetic procaine block.

One should be on the lookout for this lesion when loss of the peripheral pulses and threatened gangrene of some of the digits follow a bullet wound that has not actually divided an artery, or even when they follow such an apparently trivial injury as the insertion of a needle, during venipuncture, into the cubital space.

In this connection, Leriche and Werquin,[30] have recently called attention to the favorable effect of dividing an injured artery or resecting a considerable portion of it, as opposed to ligation in continuity. The chances of securing an effective collateral circulation are greatly improved by resection, an old contention of Leriche's, especially applicable in war surgery when arteries are likely to be extensively lacerated and thrombosed in complicated wounds. Resection tends to break up reflex vasoconstriction originating in irritation of the arterial wall and favors the development of a collateral circulation.

Arteritis

Hoyt, Perera and Kauvar[31] report 3 cases of temporal arteritis, a lesion first described by Horton, Magath and Brown.[32] This unexplained granulomatous, inflammatory disease of the temporal arteries in elderly persons is associated with serious headache and constitutional symptoms of a severity out of all proportion to the local lesion and tenderness, with redness, over the temporal vessels. No underlying causative factor has consistently been noted. In their cases, resection of a portion of the diseased artery relieved pain and favorably influenced the disease, but fever generally continued for several weeks.

Arterial Spasm Resulting from Cervical Rib (Scalenus Syndrome)

MacFee[33] calls attention to dilatation of the subclavian artery distal to the point at which it is compressed behind the scalenus anticus muscle. He found 125 cases with vascular symptoms among 360 cases of cervical rib with pressure symptoms (either nervous, vascular or both). In the particular case he describes, the brachial artery was also noted as a hard pulseless cord. Several fingertips of the cyanotic hand were gangrenous. This account recalls a very similar case reported by Clute[34] as being "acute arterial obstruction from arteritis." A very reasonable explanation of these peculiar findings has been offered by Telford and Stopford,[35] who suggest that irritation of the vasomotor nerves in the lowest cord of the brachial plexus as it passes over the first or a cervical rib is responsible for spasm and subsequent closure of the brachial artery, and it must be supposed that dilatation of the subclavian is part of the reaction. Besides freeing the structures behind the scalenus anticus muscle, the hard, cordlike brachial artery should probably be resected.

Arterial Spasm in Thrombophlebitis

The French and German literature since 1934 has contained accounts of arterial spasms that rarely occur with the onset of femoral thrombophlebitis yet may be serious enough to produce gangrene of the leg. The cause of such spasms, as Leriche and Kunlin[36] have suggested, lies in a perivascular irritation that not only throws the

adjacent artery into contraction but sets up a reflex peripheral vasoconstriction, which will be discussed in the section on thrombophlebitis. The onset of phlegmasia alba dolens is often marked by a diminution in the femoral and peripheral pulses. Rarely, all pulsations below the inguinal ligament disappear, the leg becoming white and cold, as if arterial embolism had occurred. Should the spasm persist, gangrene sets in. Should it relax, as it may very suddenly do, the whole leg becomes engorged with blood. Sympathetic block seems to have little influence on the more violent spasms, although it undoubtedly causes the milder ones to relax.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 28231

PRESENTATION OF CASE

First admission. A sixty-two-year-old single female physician was admitted to the hospital because of fever for a day following an intermittent cough of a month's duration.

Four weeks before entry, the patient had a sore throat followed in a few days by a dry hacking paroxysmal cough. The cough persisted when the soreness in the throat subsided. About a week later, the cough grew worse during the course of another few days of sore throat. The night before entry, the patient had a severe paroxysm of coughing, "wheezing on inspiration like an asthmatic." This was followed by a chill lasting three hours. She felt nauseated but did not vomit. Soreness but no actual pain developed in the right chest and was aggravated by respiration. The next day, fever was noted, and she entered the hospital.

The patient had been in the hospital five times before, with symptoms suggesting cholecystitis and renal colic. Six years before the last entry, operation disclosed right hydronephrosis due to aberrant blood vessels. These vessels were ligated, and a right nephropexy was performed. At a second operation several months later, an acutely inflamed gall bladder with a single stone was removed. These operations afforded complete relief from symptoms. Four years before the last entry, the patient had a sudden attack of severe "anginoid pain" radiating up the left side of the neck and down the left arm. This attack, which began when the patient was in bed, lasted half an hour. Dull pain and soreness remained for about three days after the acute phase. Three years before entry, there was a similar attack. This episode was not preceded by exertion. After this, the patient remained symptom free except for momentary "tight" sensations beneath the sternum "on climbing hills."

On admission, the patient appeared obese and uncomfortable, with a dry hacking cough. The hands were somewhat cyanotic. The lungs seemed clear. The heart was not remarkable.

The blood pressure was 130 systolic, 60 diastolic. The temperature was 102°F., the pulse 110, and the respirations 30.

Examination of the blood showed a white-cell count of 36,000. The blood Hinton reaction was negative. The urine showed occasional red and white cells in the sediment but was otherwise normal. Throat culture grew beta-hemolytic streptococci but no pneumococci. A blood culture was sterile.

A roentgenogram of the chest showed moderate prominence of the lung roots, without definite evidence of pneumonia.

The patient was given sulfadiazine for five days, a maximum blood level of 18 mg. per 100 cc. being attained on the second day. The temperature returned to normal on the third day, and there was a corresponding fall in the white-cell count to normal. The patient was discharged improved on the tenth hospital day.

Final admission (two weeks later). The patient remained well until five days before re-entry, when there was sudden onset of chills and fever, with severe shaking and profuse sweating. The fever was intermittent, reaching 104 or 105°F. each day. The right flank and right upper quadrant became tender. There was no headache, nausea or vomiting.

On readmission, the patient was too tired to sit up for examination. A few crepitant rales were audible at the end of inspiration over the left upper chest anteriorly and posteriorly. The heart seemed normal except for a slight systolic murmur at the apex. There was some tenderness in the left lower quadrant of the abdomen, seemingly over the sigmoid and descending colon. Posteriorly, there was tenderness over the lumbar spine and slight tenderness in the costovertebral angle on each side.

The blood pressure was 100 systolic, 60 diastolic. The temperature was 98°F., the pulse 98, and the respirations 20.

Examination of the blood showed a white-cell count of 26,400 with 95 per cent polymorphonuclears, 4 per cent lymphocytes and 1 per cent monocytes; no parasites were seen in stained smear. Agglutination tests for typhoid fever and undulant fever were negative. The nonprotein nitrogen was 41 mg. per 100 cc. The urine showed a + test for albumin and occasional red and white blood cells in the sediment. Urine and stool cultures grew no significant pathogenic organisms.

A roentgenogram of the abdomen showed considerable gas in the colon and a dilated loop of bowel consistent with ileum in the right mid-abdomen. A roentgenogram of the chest showed no definite evidence of pulmonary consolidation or of pleural effusion. A roentgenogram of the left shoulder was negative. An intravenous pyelo-

gram was normal except for slight rotation of the right kidney.

An electrocardiogram showed normal rhythm, with total inversion of Lead 5 and flattening of T_2 and T_4.

The temperature spiked to 104 or 105°F. daily for a week, the intervening swings returning to 98 or 97°F. The white-cell count ranged around 40,000, with a maximum of 75,800 on the eighth hospital day. Sulfadiazine was begun on the fourth day and continued for a week, a maximum blood level of 15.2 mg. per 100 cc. being reached. On the seventh hospital day, the liver edge became palpable and tender. Two days later, the liver edge extended 4 cm. below the costal margin. There was no jaundice. A bromsulfalein test showed 35 per cent dye in serum. On the eighth hospital day, the patient complained of difficulty in breathing. The respirations were 28 and shallow. Fine and medium rales were heard at both bases. The abdomen was moderately distended. Roentgenograms showed no evidence of pulmonary consolidation. The liver shadow was larger than it had been on previous examination. On the twelfth hospital day, there seemed to be a slight increase in intensity of the systolic murmur, which was also heard in the aortic area. On the same day, a culture of blood that had been taken on the third hospital day showed a Type 7 pneumococcus, and the patient was given 170,000 units of type-specific rabbit antiserum. Four more blood cultures became positive for Type 7 pneumococcus. Because of hematuria and marked reduction in the output of urine, chemotherapy was discontinued on the twelfth day. The following day, cystoscopy showed that no urine was coming from the right ureter, and only a small flow from the other kidney.

The patient continued to decline, dying on the fifteenth hospital day.

Differential Diagnosis

Dr. Marian W. Ropes: The electrocardiographic findings might be significant in view of the anginal pain, but I am ascribing them to the position of the heart in this obese person, with a high diaphragm and some abdominal distention.

It is interesting that the urinary shutdown, if due to sulfadiazine, came at a more logical time than that in the case discussed by Dr. Talbott.* It was on the twelfth day and could, in the case under discussion, be ascribed to crystal deposition. However, there is no evidence of such deposition in the form of demonstrated crystals in the urine.

*Case records of the Massachusetts General Hospital (case 28211). *New Eng. J. Med.* 226:861-864, 1942.

The one definite fact in this case is that the patient had pneumococcal septicemia and died therefrom by way of a urinary complication. Beyond this, it is difficult to speak with much certainty. The important points to be determined are the portal of entry, the areas of localization that might be responsible for the organisms found later in the blood stream, and whether a diagnosis besides pneumococcal infection needs to be made.

To consider the third question first, an underlying malignant lesion should be mentioned. The symptoms of the first four weeks could presumably be associated with bronchiogenic carcinoma, or some other pulmonary tumor. However, the x-ray films and clinical course give no support to such a diagnosis. Metastatic cancer in the liver could explain the right-upper-quadrant symptoms, the enlargement of the liver and, possibly, the bromsulfalein retention, but could not explain the rest of the picture. There is no indication of lymphoma or similar tumors. But if one tries to ascribe the whole picture to pneumococcal infection, certain aspects are difficult to explain. Definite invasion of the blood stream apparently occurred on the night before admission, with a temporary bacteremia, because the blood culture taken soon thereafter was negative.

The next point to consider is where the organisms localized as a source for the organisms found later in the blood stream. There are three possible areas of localization: the kidneys, liver and heart valves. The previous kidney abnormality, the previous operation and some evidence of renal insufficiency suggest the possibility of localization of organisms in the kidney. There is no evidence of pyelonephritis, — nothing on which to base a diagnosis of renal abscesses, — and as I have mentioned, the terminal events could and, I think, should be ascribed to the sulfadiazine therapy. The enlargement of the liver and the bromsulfalein retention of 35 per cent in the absence of jaundice are very difficult to explain on any diagnosis. If the statement of bromsulfalein retention is accurate, one might attempt to ascribe it to secondary hepatitis, but one would expect jaundice. One would think that such rapidly developing retention as this might indicate previous liver damage, suggested possibly by the long story of cholecystitis, but here again the absence of jaundice is inconsistent. If liver abscesses were the only areas of localization of the organisms, it would be somewhat unlikely for the blood cultures to be persistently positive.

The positive cultures point to endocarditis as the most probable localization of the pneumococci. The cardiac findings, however, are unimpressive

and give little evidence concerning the valves involved. The increasing intensity of the systolic murmur at the time of the second admission and the slight evidence of increasing pulmonary congestion suggest mitral-valve involvement. The enlargement of the liver, if not ascribable to pneumococcal involvement, suggests tricuspid involvement. We do not know whether the liver pulsated and whether the neck veins were distended. Furthermore, the question whether the valves involved by endocarditis were previously abnormal is difficult to answer. There is no evidence of previous cardiac involvement except a suggestive history of anginal pain. This does seem fairly definite, and I believe that the patient had angina but no evidence of other cardiac abnormality, and we have no evidence of previous valvular involvement. Therefore, in summary, in determining the area of localization of the pneumococci and the part played by the kidney in the picture, I believe that the organisms were localized on the heart valves and not in the liver, that the liver involvement was secondary thereto, and that the acute kidney involvement was secondary to sulfadiazine therapy. There might also be, of course, abscesses in the liver.

DR. GREENE FITZHUGH: This was a difficult case as we followed the patient along. We found pus in the urine, but it was an uncatheterized specimen. We considered the possibility of perinephritic abscess. We went through a period of uncertainty about liver infection. Then, with the positive blood cultures, we believed that it was definitely endocarditis.

DR. EDWARD F. BLAND: May I ask what the clinical impression was when the patient was discharged from the hospital the first time?

DR. FITZHUGH: I signed the discharge slip with a diagnosis of pneumonia. X-ray examination never showed anything, and the sputum showed no pneumococci. Here was a person with three weeks' cough and a temperature of 102°F. who was apparently cured by sulfadiazine. Looking back on it, I think that was the beginning of this illness.

DR. AUBREY O. HAMPTON: The interesting x-ray features are all concerned with films taken during previous admissions. We examined the gall bladder four times, when the Graham test was negative and the pyelogram positive. Thus, even though the history suggested gallstone colic, the surgeons operated on the kidney. When the patient returned home, she had the same type of attack that she had been having, and we made another gall-bladder examination that was again entirely negative. At the second operation, a single stone was found, not in the gall bladder but in the cystic duct.

DR. FLETCHER H. COLBY: I operated on the right kidney. The patient had a definite congenital abnormality of the blood supply of the kidney, with a small degree of hydronephrosis, and we were quite pleased that we had relieved her of pain. As Dr. Hampton has said, she went home and promptly had a typical attack of gallstone colic. Attention, of course, was fixed on the right kidney region. Then, the patient came back with unexplained fever and marked severe chills every few hours, and we were not at all certain that she did not have infection in the right kidney or perirenal abscess. An intravenous pyelogram showed that the right kidney was functioning well and that there was not the degree of hydronephrosis that had been present before; the kidney outlines and the psoas muscles showed clearly enough. Consequently, we eliminated the possibility of infection in the kidney, and we believed that the trouble was probably due to blood-stream infection in spite of the negative blood cultures, which subsequently became positive.

I think it should also be brought out that the patient was given not only sulfadiazine but also sulfathiazole. We gave her sulfadiazine because she had done so well on it before. We thought it was a continuation of the previous disease. This time, the patient did not respond, and we therefore changed to sulfathiazole. On the sixth or seventh day of sulfathiazole therapy, there were gross hematuria and many crystals in the urine sediment.

DR. CHAMP LYONS: I saw this patient with Dr. Fitzhugh, and at that time I raised the question whether renal infarction was responsible for the urinary findings. I do not know what was eventually found. It seems to me that a patient with persistent hematuria and urinary shutdown due to sulfathiazole should show crystals. The crystals were not prominent at the time I saw the patient. I take it that the hematuria persisted after the crystals disappeared.

DR. COLBY: The patient did have crystals until she died. Every specimen had them until the last few days.

DR. ALLEN G. BRAILEY: How often does one have chills of this character with endocarditis?

DR. LYONS: Any intermittent bacteremia gives chills.

DR. ALLAN M. BUTLER: Was there any impression regarding the possibility of cardiac failure?

DR. TRACY B. MALLORY: I do not believe that was seriously considered. Dr. Chester M. Jones at one time was very much enamored with the idea of liver abscess but gave that up at a later period.

DR. LYONS: This whole business of hepatitis is a problem of much interest. We studied 68 patients last spring by prothrombin levels and bromsulfalein retention, and found that 20 per cent of those receiving chemotherapy for acute infection developed some evidence of impaired prothrombin time or bromsulfalein retention and that jaundice was not a regular accompaniment. That type of hepatic disturbance remains to be elucidated.

CLINICAL DIAGNOSIS

Acute bacterial endocarditis, Type 7 pneumococcus.

DR. ROPES'S DIAGNOSES

Pneumococcal endocarditis.
Ureteral obstruction from sulfadiazine crystals.

ANATOMICAL DIAGNOSES

Endocarditis, bacterial (Type 7 pneumococcus).
Renal infarction, complete, right kidney.
Splenic infarction, small.
Nephritis, focal glomerular, acute.
Arteriosclerosis, aortic and coronary, minimal.
Operative scars: nephropexy, cholecystectomy.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Post-mortem examination did show a pneumococcal endocarditis of the mitral valve. There was a very large vegetation, 2 cm. in diameter, on the right cusp. This had evidently given off emboli, and one of considerable size was found in the right renal artery, so that the right kidney was totally infarcted. There was also an infarct in the spleen. The left kidney was somewhat swollen. It was examined with great care for crystals. None could be found in the pelvis or the ureter on that side. On the other hand, some crystals were seen in the pyramid. These were teased out, but did not look like the crystals of any of the sulfonamides and proved to be urates. The glomeruli in this case were also abnormal. The glomerulonephritis was somewhat uneven in distribution — very marked in some glomeruli and relatively less marked in others. Of course, glomerular involvement can occur with any form of bacterial endocarditis, so that this is perhaps to be regarded as a very diffuse form of so-called "embolic glomerulonephritis" rather than a true diffuse glomerulonephritis.

The coronary arteries were entirely normal, and there was no hiatus hernia; nothing else was found to explain the attacks of anginal pain. The liver was slightly large and mottled, but showed no demonstrable hepatitis.

CASE 28232

PRESENTATION OF CASE

A forty-three-year-old shipping clerk was admitted to the hospital because of vomiting and associated abdominal cramps.

He was well until about eight weeks before entry, when he was awakened from sleep by severe cramping pain in the upper abdomen. He vomited part of his supper, together with some peanuts that he had eaten shortly before retiring an hour and a half earlier. There was no further difficulty until two weeks later, when the patient was again seized with severe, shooting epigastric cramps and vomited peanuts eaten an hour earlier. The vomiting was spontaneous and was not accompanied by nausea. It relieved the pain promptly. A physician prescribed belladonna and Amphogel, with restriction of the diet. Subsequently, the patient vomited two or three times a week, with associated pain but no nausea as before. He felt weak and therefore stopped working. He was referred to the Out Patient Department, where physical examination was essentially negative. Roentgenograms of the esophagus, stomach, duodenum and small bowel were likewise negative. The patient was advised to continue his dietary restrictions and his medication. In the four weeks preceding entry, the vomiting became more frequent and severe. The patient often vomited greenish bitter fluid an hour or an hour and a half after breakfast and after lunch. In the week before entry, such vomiting and abdominal cramps followed every meal. Small amounts of bright-red blood were spat up after vomiting. The patient lost 20 pounds of weight during the illness.

The appendix had been removed six years before entry. The past history was otherwise irrelevant.

On admission, the heart and lungs were normal. The abdomen showed slight deep epigastric tenderness but no masses or palpable viscera. Rectal palpation was essentially negative.

The blood pressure, temperature, pulse and respirations were normal.

Examination of the blood showed a red-cell count of 4,600,000 with 85 per cent hemoglobin, and a white-cell count of 8700 with 64 per cent polymorphonuclears. The serum protein was 6.5 gm. per 100 cc. The chlorides were 85.6 milliequiv. per liter, rising to 98.5 milliequiv. Gastric analysis showed 8.0 units of free acid and 9.5 units of total acid (fasting), with no appreciable increase after histamine. The stools were strongly positive for occult blood. The urine was normal.

A roentgenogram of the abdomen showed old residual flecks of barium in the lower descending

colon, possibly in diverticulums. There was considerable gas in the stomach. A repeat roentgenologic examination of the gastrointestinal tract showed a normal esophagus and stomach. The second portion of the duodenum was somewhat dilated, and there was slight delay at the junction of the second and third portions of the duodenum. The third portion was poorly filled and included a crater 1 cm. across, with surrounding induration and probable mucosal destruction. There were several intraluminal defects in the left half of the large bowel suggesting either fecaliths or polyps.

On the ninth hospital day, an operation was performed.

Differential Diagnosis

Dr. John R. Graham: The final x-ray pictures have shown us a definite lesion in the third portion of the duodenum, although the first series failed to reveal any abnormalities. It seems to me that a lesion in this situation would adequately explain the symptoms of vomiting and epigastric pain. The ulcerations mentioned in the last x-ray report could explain the positive guaiac test in the stools, although one would have to think that the patient could not have had a strongly positive guaiac test for very long without more anemia than the blood count showed.

Dr. George W. Holmes: The fact that they had taken a number of films of this area showed that they were interested in it. The obstruction at the lower portion of the duodenal loop where it joins the ileum is obvious in a number of films, all of which show barium delayed at that point. I suspect that this is what they thought was the ulcer. There is also an unusual amount of gas in the small bowel in some of the films. The colon is normal. The stomach, so far as I can see, is normal. From the evidence I have here, one can say only that there was a definite delay in the passage of the barium meal from the duodenal loop into the jejunum. In one film, it looks like an ulcer.

Dr. Graham: Between the duodenal loop and the jejunum?

Dr. Holmes: Yes.

Dr. Graham: As I have said, I think the lesion explains the symptoms, and my job is to guess the histology of the lesion. It has certain characteristics, which we can learn from the history and the x-ray pictures. The x-ray films tell us that the lesion was ulcerative, that it had an area of induration around it, and that the mucosal pattern of the bowel showed evidence of being destroyed. I think those things suggest the presence of a malignant lesion, probably one arising in the bowel itself. There is evidence, in the history and perhaps in the x-ray examination, that this lesion progressed rather rapidly. The whole illness lasted only eight weeks, the symptoms and signs growing rapidly worse during the course of the last month. The x-ray films taken at the end of one month of symptoms failed to reveal dilatation or evidence of obstruction or any lesion that could be seen, whereas those taken after two months of symptoms showed definite trouble. Further evidences against an inflammatory lesion were the normal temperature and the normal white-cell count. The x-ray report mentioned the possible presence of polyps in the colon, which suggest that the patient might have had polyps elsewhere, even in the duodenum. Dr. Holmes, however, doubts the evidence of polyps.

I think the main thing to think of in identifying this lesion is whether it was a carcinoma of the duodenum near the junction of the jejunum, or a lymphoma. We also have to think about a peptic ulcer, since an ulcer was definitely demonstrated. It seems to me that the location of the lesion, the low gastric acidity and the duration of the symptoms are distinctly against an ordinary duodenal or peptic ulcer. One would think about syphilis, but they probably would have helped us out with the Hinton report. There was no history of syphilis. Could the condition have been regional enteritis? On the whole, I lean away from an inflammatory lesion and think that the most likely diagnosis is a carcinoma in that part of the bowel. The second on my list is lymphoma, and I shall simply mention in passing the possibility of polyp that has undergone malignant degeneration, the only reason for that thought being the doubtful presence of polyps elsewhere in the intestinal tract.

Dr. Chester M. Jones: It seems to me that the first x-ray film did not show anything because it was routine. I think that is a fair statement, but I should like to have Dr. Holmes comment on it. Very frequently, unless the radiologist is asked to look for a definite lesion, he may on routine examination overlook a lesion in the third portion of the duodenum. This lesion may well have been there a month before.

Dr. Holmes: I agree with you, and should like to emphasize the fact that clinicians should tell the radiologist what they have in mind before asking for the x-ray report. One does not see things one does not look for.

Dr. Jones: I have seen only a small number of cases of cancer of the terminal ileum, upper jejunum or the lower duodenum. With the history, not of epigastric pain but of umbilical pain, one is given the clue. The lesion should lie in the small bowel well below the mid-duodenum, and one has the right to ask Dr. Holmes to look for it.

DR. GRAHAM: One must consider the possibility of a malignant lesion, extrinsic to the bowel, something to do with the pancreas. However, I thought that the directness with which the symptoms were connected with the lesion and the ulceration were against that.

DR. TRACY B. MALLORY: Can you say anything from the x-ray point of view concerning the possibility of pancreatic tumor?

DR. HOLMES: I think it is a decided possibility; narrowing and obstruction in that part of the duodenum not infrequently are due to cancer arising in the pancreas. The absence of a gross deformity of the duodenal loop does not rule out cancer of the pancreas. I used to think a deformed loop was necessary. But that is not so.

CLINICAL DIAGNOSIS

Duodenal cancer?

DR. GRAHAM'S DIAGNOSIS

Carcinoma of duodenum.

ANATOMICAL DIAGNOSIS

Carcinoma of pancreas, invading duodenum.

PATHOLOGICAL DISCUSSION

DR. MALLORY: This patient was explored, and a localized tumor was found in the pancreas in about the midportion. It had invaded the duodenal wall and had produced a small papillary mass in the duodenum, but no ulcer that I could find. A gastroenterostomy was done, and a biopsy of the pancreas showed perfectly normal pancreatic tissue. However, the patient did not long survive gastroenterostomy, and at postmortem examination we were able to confirm the diagnosis of cancer in the pancreas.

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The office of the Medical Officers' Recruiting Board of Massachusetts is located at 319 Longwood Avenue, Boston (telephone, ASP 3638); all physicians who desire commissions as medical officers in the Army of the United States should immediately communicate with the officers in charge.

ANNUAL MEETING

The one hundred and sixty-first annual meeting of the Massachusetts Medical Society, held May 25, 26 and 27 at the Hotel Statler, Boston, resulted in the largest registration of members, 1556, in the history of the Society, in spite of the fact that several hundred of those who, in the past, have regularly attended these meetings are now away from Massachusetts, serving as medical officers in the United States Army and Navy. The luncheon meetings of the sections were well attended, but there was a distinct drop in the registration of wives, undoubtedly owing to the limitations to the program arranged by the Ladies' Committee that were necessitated by lack of transportation facilities. Never before have there been so many scientific and technical exhibits; the Ballroom and Ballroom Assembly of the Hotel Statler, however, are so well adapted for exhibits of this sort that both the members and the exhibitors were more than pleased with the arrangement.

The new schedule calling for the annual meetings of the supervising censors and of the Council during the late afternoon and evening of the day preceding the opening of the general sessions worked out very satisfactorily. The main items of business at the meeting of the Council comprised reports of the standing and special committees and the appointment of new committees. The following officers were elected for the year 1942–1943: president-elect, Roger I. Lee, of Boston; vice-president, Peirce H. Leavitt, of Brockton; secretary, Michael A. Tighe, of Lowell; treasurer, Charles S. Butler, of Boston; and orator, Edward P. Bagg, of Holyoke. Some controversy arose concerning the procedure to be adopted regarding graduates of approved medical schools who are in or about to enter the United States Army or Navy and who desire to become members of the Society; the matter was referred to the recessed meeting of the Council on the following day, and at that time, the Society, at its annual meeting, having voted to waive, for the duration of the present emergency, the by-laws relating to the timetable governing applications for membership from such graduates, two physicians whose applications were irregular were admitted to membership. At the same recessed meeting, Dr. Eliot Hubbard, Jr., of Cambridge, was elected assistant treasurer.

The annual meeting of the Society was unusually long, chiefly owing to considerable discussion concerning the proposed by-laws. Several members

opposed two of the regulations—that requiring five-year licensure in the United States before a graduate of a foreign medical school can apply for membership in the Society and that specifying that the Committee on Nominations shall cause its report to be published in the notice of the annual meeting of the Council; however, both these sections were passed by a vote of hands, and all the others by practically unanimous consent. At the close of the business meeting the incoming president, Dr. George Leonard Schadt, of Springfield, was introduced. Following the meeting, Dr. William B. Castle, of Boston, delivered the annual oration, "Some Remarks on Therapy for Anemia," which appears elsewhere in this issue of the *Journal*.

Dr. Frank H. Lahey, of Boston, president of the American Medical Association, and Dr. Morris Fishbein, of Chicago, editor of the *Journal of the American Medical Association*, were the speakers at the annual banquet, which was attended by over 500 members and guests. Both emphasized the great need for young physicians in the armed forces, urged all under forty-five years of age to volunteer and warned that conscription will inevitably follow if the voluntarily enlisting personnel proves insufficient. The banquet was followed by the Shattuck Lecture, "Medicine and Air Supremacy."* The speaker, Dr. John F. Fulton, of New Haven, Connecticut, stressed the role that medicine has played in the development of combat aviation, particularly regarding the problems brought about by high-altitude flying, crashes and the care of pilots after injury; he predicted that within a year *nearly twenty thousand* flight surgeons and aviation medical officers will be needed in the Army Air Forces.

The majority of the papers read at the general sessions concerned one or another aspect of medicine as applied to the present emergency. Various problems of civilian defense were discussed, and mumps, tropical diseases, venereal diseases, skin diseases, head injuries, industrial health and mass immunization were considered in relation to the war effort. Other speakers commented on the effects of the war on public-health problems, medical education and American medicine in general, and the program was concluded by a symposium covering minor psychiatric disturbances in war and in civilian life.

All in all, the meeting was eminently successful, and one that will be remembered for many years by those who attended.

*Fulton, J. F. Medicine and air supremacy. *New Eng. J. Med.* 226:873-880, 1942.

THE COMMONWEALTH FUND

In its twenty-third annual report, the Commonwealth Fund gives an account of its current effort to "do something for the welfare of mankind," in accordance with the wish of its founder, Mrs. Stephen V. Harkness. A total of $1,841,332 was appropriated for philanthropic purposes during the past year.

The policy of the fund paralleled that of previous years, in spite of adjustments made necessary by the war. Although the British fellowships offered since 1925 were suspended, although many members of nursing and medical staffs aided by the fund were called to military duty, and although a research project that had made great contributions to the knowledge of kidney function was halted because key workers went into national service, most of the undertakings progressed toward the goal of health maintenance and scientific advance. Subsidies and consultant services were furnished in twenty-eight states to encourage research and high standards of teaching in medical schools, to enrich and extend rural health services, to provide or improve hospital facilities in rural districts, and to furnish and reinforce community opportunities for mental-health services. The fund subsidized departments of preventive medicine at five medical schools and a department of psychiatry at another. A grant was made to the Peter Bent Brigham Hospital in Boston for the enlargement of its psychiatric service.

Since the war began, the fund has contributed $685,000 for war relief and related activities. An epidemiologic unit, maintained by the fund in cooperation with Harvard University and the American Red Cross, is operating a hospital and field service for the control of communicable disease in England. And, through the British War Re-

lief Society, support of the American Hospital in Britain has been maintained. The mental-health services for children, provided through the Child Guidance Council, have proved their worth in the care and adjustment of the helpless victims of wholesale bombings.

Thus, in spite of curtailments demanded by the exigencies of wartime, the Commonwealth Fund continues its aid of scientific advance and its measures to relieve misery. Its zealous and humane efforts are an inspiration in a world in which the ideals of mercy and disinterest are challenged and must be fought for. The directors of the fund may well be proud of what has been achieved. Those who fight and those "who only stand and wait" may be content that the torch of progress is in such hands.

MEDICAL EPONYM

Pasteur Treatment

Louis Pasteur (1822-1895) reported his "Méthode pour prévenir la rage après morsure [Method of Preventing Rabies after Bites]" at the meeting of the Académie des Sciences on October 26, 1885. The memorable account of its first application appears in the *Comptes rendus hebdomadaires des séances de l'Académie des sciences* (**101**:765-772, 1885). A portion of the translation follows:

> After innumerable experiments, I have arrived at a prophylactic method that is practical and rapid, whose success in dogs has already been frequent and certain enough to make me confident of its general applicability to all animals and to man himself. This method is based essentially on the following facts:
>
> Inoculation of a rabbit by trepanation under the dura mater with rabic spinal marrow from a mad dog always transmits rabies to the animal after an average incubation period of about fifteen days.
>
> If virus from the first rabbit is transferred by this method to a second, from this to a third and so on, there will soon be apparent a progressively increasing tendency to a diminution of the incubation period for rabies in the successively inoculated rabbits. . . .
>
> The spinal cords of these animals are rabic throughout their extent, with a constant virulence.
>
> If pieces a few centimeters in length are taken from these cords with all possible precaution regarding cleanliness, and if these are suspended in dry air, their virulence slowly disappears completely. . . .
>
> These facts being established, let us consider the method of rendering a dog immune to rabies, in a relatively short time.
>
> A piece of fresh rabic cord from a rabbit killed by rabies, developed after seven days' incubation, is suspended daily in one of a series of flasks, the air in which is kept dry by pieces of potash placed at the bottom of the flask. Each day, moreover, a Pravaz syringe full of sterilized bouillon, into which has been incorporated a small piece of one of these dried cords, is injected under the skin of the dog, beginning with a cord the date of which is a sufficient number of days before the day when the operation is performed so that one may be sure the cord is not virulent. . . . On subsequent days, more recent spinal cord is used, separated by intervals of two days, until at last a very virulent cord is reached, which has been in the flask only a day or two.
>
> The dog is now immune to rabies. He may be inoculated with rabic virus under the skin or even on the surface of the brain by trepanation, without the development of rabies.
>
> By the application of this method, I had succeeded in obtaining 50 dogs of all ages and breeds that were immune to rabies, without having met with a single failure, when there presented themselves unexpectedly in my laboratory, on Monday, July 6 last, three persons from Alsace: Theodore Vone, a grocer of Meissengott near Schlestadt, who had been bitten in the arm on July 4 by his own dog, which had gone mad; Joseph Meister, aged nine years, also bitten on July 4, at 8 o'clock in the morning, by the same dog. This child had been thrown to the ground by the dog and showed a number of bites on his hand, legs and thighs, several quite deep, that made it difficult for him even to walk. . . . The third person, who had not been bitten, was the mother of little Joseph Meister. Mr. Vone had severe bruises on his arms, but he assured me that his shirt had not been pierced by the fangs of the dog. Since he had nothing to fear, I told him he might return to Alsace the same day, which he did. Little Meister and his mother I kept with me, however. . . .
>
> The death of this child seeming inevitable, I decided, not without keen and tormenting doubts as may well be supposed, to try on Joseph Meister the method that had always succeeded in my hands with dogs.
>
> Therefore, on July 6, at 8 o'clock in the evening, sixty hours after the bites on July 4, in the presence of Drs. Vulpian and Grancher, the lad Meister was inoculated beneath a fold of the skin in the right hypochondrium, with a half Pravaz syringe of bouillon containing spinal cord from a rabbit dead of rabies on June 21, which had been kept since that time — that is, for 15 days — in a flask of dry air.
>
> On subsequent days, further inoculations were made, always in the hypochondria, as shown in the following table:

July 7,	9 a.m.	Cord of June 23 (14-day cord)
July 7,	6 p.m.	Cord of June 25 (12-day cord)
July 8,	9 a.m.	Cord of June 27 (11-day cord)
July 8,	6 p.m.	Cord of June 29 (9-day cord)
July 9,	11 a.m.	Cord of July 1 (8-day cord)
July 10,	11 a.m.	Cord of July 3 (7-day cord)
July 11,	11 a.m.	Cord of July 5 (6-day cord)
July 12,	11 a.m.	Cord of July 7 (5-day cord)
July 13,	11 a.m.	Cord of July 9 (4-day cord)
July 14,	11 a.m.	Cord of July 11 (3-day cord)
July 15,	11 a.m.	Cord of July 13 (2-day cord)
July 16,	11 a.m.	Cord of July 15 (1-day cord)

> . . . . Nine rabbits were inoculated by trepanation with the various cords used so that the state of virulence of these cords might be followed.
>
> During the last days, I had thus inoculated Joseph Meister with the most virulent rabic virus. . . .
>
> He had escaped, not only the rabies that his bites would have caused to develop, but that with which I had inoculated him as a control of the immunity conferred by that treatment — a rabies more virulent than that of the mad dog. . . . From the middle of August, I viewed with confidence the future health of Joseph Meister. Today, three months and three weeks after the accident, his health remains all that could be wished.

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

CASE HISTORY: FATAL MYELOGENOUS LEUKEMIA IN PREGNANCY

A twenty-eight-year-old married woman, whose past history was very incomplete, was transferred immediately to the hospital by the physician who saw her when she was six and a half months pregnant. On admission she was practically moribund. There was no history of prenatal care, but the patient had had anemia for some years. During the week before entry into the hospital, there had been increasing weakness, with multiple subcutaneous hemorrhages. Examination revealed marked pallor, a rapid, weak pulse, low blood pressure and a uterus just above the umbilicus. The urine was normal. Examination of the blood showed characteristic signs of myelogenous leukemia. There was no statement in the record about the size of the spleen. The patient, who was not in labor, died undelivered a few hours after entry. No autopsy was performed.

Comment. Myelogenous leukemia in itself is a rare disease, and its association with pregnancy is, of course, extremely rare. The general dictum of such a complication would obviously be to interrupt the pregnancy, because pregnancy would only aggravate the disease. That interruption would do anything except prolong life is undeniable.

Patients suffering from such blood diseases as myelogenous leukemia and pernicious anemia ordinarily do not become pregnant. Certainly, they should be advised against pregnancy.

DEATHS

DOW — DAVID C. DOW, M.D., of Cambridge, died May 27. He was in his sixty-eighth year.

Born in Cambridge, Dr. Dow received his degree from Tufts College Medical School in 1898. He was an intern at Cambridge Hospital, where he was a member of the staff until his retirement a year ago. He was medical examiner of the first district of Middlesex County, and was a member of the Massachusetts Medical Society and the American Medical Association.

His widow, a son and a daughter survive him.

NEFF — IRWIN H. NEFF, M.D., of Detroit, died recently. He was in his seventy-fourth year.

Dr. Neff received his degree from University of Maryland School of Medicine and College of Physicians and Surgeons in 1889. He was a former superintendent of the Foxboro and Norfolk State hospitals, and was a former member of the Massachusetts Medical Society.

WAR ACTIVITIES

UNITED STATES ARMY

Base Hospital No. 6, recruited from the staff of the Massachusetts General Hospital, was recently ordered to active duty. The officer personnel is as follows:

Commanding Officer: Colonel Thomas R. Goethals.

Surgical Service: Lieutenant Colonel Horatio Rogers, chief.

Medical Service: Lieutenant Colonel Donald S. King, chief.

Majors: William T. S. Thorndike (registrar), Marshall K. Bartlett, Edward F. Bland, Henry H. Faxon, Trygve Gundersen, James A. Halsted, Sylvester B. Kelley, Alfred Kranes, Langdon Parsons, Robert G. Rae, Charles L. Short, Grantley W. Taylor, Jackson M. Thomas, Edward G. Thorp, John H. Talbott, James R. Lingley (chief, X-Ray Service) and James H. Townsend (chief, Section of Communicable Diseases).

Captains: Otto E. Aufranc, Francis H. Chaffee, Richard J. Clark, Lowrey F. Davenport, Daniel C. Dawes, Joseph H. Demers, John R. Frazee, John R. Graham, Thomas S. Hamilton, Henry M. Heyl, Daniel J. Holland, Theodore H. Ingalls, Alfred O. Ludwig, Otto D. Sahler, Spiros P. Sarris, Hermann B. F. Seyfarth, Oscar S. Staples, Somers H. Sturgis, Howard I. Suby, Eugene R. Sullivan, Garrett L. Sullivan, Howard Ulfelder, Claude E. Welch, Richard G. Whiting and John W. Zeller.

First Lieutenants: William E. Arnold, Robert M. Bailey, Edwin L. Canton, Calvin R. Coggins, Daniel S. Ellis, Marlow B. Harrison, Knowles B. Lawrence, Claude E. McGahey, John B. McKittrick, Sedgwick Mead, Frederick K. Poulin, Stanley W. Wyman and William C. Burrage.

CORRESPONDENCE

PELLAGRA NOT A REPORTABLE DISEASE

To the Editor: At a meeting of the Department of Public Health on May 12, 1942, it was voted to remove pellagra from the list of reportable diseases. This action was taken because the disease has a very low prevalence in Massachusetts and the information which was being received from the reports was serving no useful purpose.

PAUL J. JAKMAUH, M.D.
Commissioner of Public Health
State House
Boston

REPORTS OF MEETINGS

BOSTON ORTHOPEDIC CLUB

A regular meeting of the Boston Orthopedic Club was held at the Boston Medical Library on January 19, with Dr. Otto J. Hermann presiding. The subject of the evening was "The Medical and Surgical Aspects of Gout."

The medical aspect was discussed by Dr. John Talbott, of the Massachusetts General Hospital. This disease is infrequent but not rare, and is usually undiagnosed for the first few years of its existence because its characteristic manifestations appear only in the later stages. This is in spite of the fact that the diagnosis is easily confirmed.

Gout may occur at any age from six to over seventy. There is periodic pain in multiple joints, with asymptomatic periods between attacks. At first, there are no residual manifestations, but later the interarticular changes brought about by the deposition of sodium urate appear. Although the resulting disabling symptoms may occur early in the disease, they never occur at the first attack. Any joint may be the site of attack, and the appearance of the joint in the acute stage closely resembles that in acute rheumatic fever or infection. A spread of the process may simulate cellulitis, but the skin is usually tense and cyanotic rather than red. Pitting edema and desquamation are occasionally encountered. There may be alimentary or genitourinary prodromes, and an attack may occur while a patient is on accepted treatment. Sometimes a high-purine meal, recent surgery, an alcoholic bout, acute infection or trauma is the only initiating factor of an attack, and the interval between such an event and the onset may vary from a few hours to days. Each bout may last days to weeks, but there is usually a prompt response to colchicine. The interval between episodes may be as long as a decade at first, but subsequent attacks become more frequent. The association of bouts of pain with changes in weather is a real one. This has been explained by the finding that these patients have a diuresis shortly before the onset of joint symptoms, with a paradoxical gain of weight. When the barometric pressure is falling before a storm, a decrease in the insensible loss of fluid from the skin accounts for this apparent discrepancy.

The diagnosis of advanced tophaceous gout, with its tophi, increased blood uric acid content and punched-out areas of bone roentgenologically, is easily made. But it is essential to discover the early cases and thus possibly prevent some of the later sequelae by appropriate therapy. A presumptive diagnosis should be made on the history of repeated attacks of polyarthritis with no interval manifestations, a family history of gout, the excretion of urate crystals and a favorable response to colchicine therapy. The finding of a constantly elevated serum uric acid content is confirmatory evidence. The differential diagnosis involves practically all joint diseases, and any chalky secretions should be examined microscopically. For the determination of the uric acid levels, serum or plasma is preferable to whole blood, for the results are higher and the difference between normal and pathologic levels more definite. By this method, most normal patients have values below 5 mg. per 100 cc., whereas gouty patients are invariably above 6 mg. In 100 cases of gout in which 900 uric acid determinations were carried out at all stages of activity and quiescence in the past eight years, the level was over 6 mg. per 100 cc. in 99 per cent, with a variation from 5.7 to 16.0 and an average of 8.8. In 400 control determinations, the uric acid values were less than 6 mg. per 100 cc. in over 96 per cent, with an average of 4.1. Other conditions that may have a high value are renal insufficiency and leukemia. It is well known that many gouty patients have the former, and it should not be forgotten that leukemic patients may have other forms of arthritis. X-ray study is probably the least helpful in diagnosis, for the lesions are characteristic neither in place nor in kind. This aid should merely be used in suspected cases but not to rule the disease in or out of itself.

There is no known cure for gout, and residuums persist unless surgically removed. An asymptomatic period should not be accepted as a cure, but the condition may be fairly well controlled in most cases by the judicious use of appropriate therapy. The acute attack may be relieved by bed rest, high-fluid intake, soft-solid diet, a cradle over the part, sedation and colchicine. The drug is best employed in the crystalline form in doses of 1/120 gr. every hour or two for eight to twelve times. Adequacy of dosage may be judged in the novice by the onset of nausea, vomiting and diarrhea, but the veterans know their capacity fairly well and can usually avoid these toxic manifestations. Improvement is evident in twenty-four to forty-eight hours, and repetition of a course of therapy should never be undertaken in less than two or three days. Otherwise, there will be toxic symptoms with a few doses and no relief of the gouty pains. There are no untoward reactions, sensitivities or the development of tolerance.

Treatment between attacks is almost impossible to evaluate because of the lack of a yardstick. Although the use of a low-protein and low-purine diet seems theoretically sound, its practical value is apparently exaggerated. Alcohol is not forbidden these patients despite its alleged role as an inciting factor. Cinchophen and its derivatives are banned because of the danger of liver damage and because it is not considered indispensable where colchicine is available. The use of mercury diuretics to cause an outpouring of fluid and urates was compared with a simple adenectomy in a case of lymphoma. Colchicine may be administered from every sixth day to every day, depending on the number of attacks each year, and this serves to keep the patient aware of both the disease and the drug; intensive therapy can thus be begun early in the prodromal stage. A high-fluid intake, as well as a reducing diet in obese patients, seems desirable, to relieve strain on affected joints. A high-vitamin and high-mineral diet is recommended, but no specific factor can be suggested as prophylactic.

Before discussing the surgical aspects of this diease, Dr. Robert Linton reviewed the history of gout in its relation to surgery. His cases were all in the late stages, and the procedures were often unorthodox from an orthopedic standpoint. The results were of course local and had no effect on the disease as a whole. The reasons for operation were pain, deformity and intractable ulcers. Before 1935, there were only seven operations at the Massachusetts General Hospital for the tophaceous deposits of gout, whereas between 1935 and 1941 Dr. Linton performed ninety-three operations on 11 patients. Formerly, the acute gouty joint was considered similar to that of an acute inflammation, and this was one factor in deciding against surgery. Another point, which has since been disproved, was the alleged lack of an adequate blood supply in gouty lesions. Dr. Linton has also found a decrease in the expected number of recurrences instead of the opposite. Eight patients were over fifty years of age, and 7 had had gout for over twenty years. The site of the operations — an indication of the relative prevalence of the condition — was as often in the hands as in the feet. The commonest type of growth was that involving the tissues down to but not including the bones and joints. Surprisingly, a third of the operations involved only the subcutaneous tissues and bursas. The notorious great toe was involved in only 5 per cent of all operations. The results in general were good, so far as relief of pain, decrease of deformity and increase of the function of the part were concerned. Healing was remarkably good, since sepsis occurred in only 3 per cent of cases, which were often ulcerated from the beginning. Several open lesions healed by primary union. It is necessary to institute measures to prevent the onset of acute attacks two to five days postoperatively, and colchicine in the usual doses three or more times a day for three days is sufficient. One important point of surgical technic is the use of transverse rather than longitudinal or elliptical incisions, even if multiple incisions then become necessary.

The discussion was opened by Dr. S. J. Thannhauser, of the Boston Dispensary. He stated that the polyarticular form of gout is much commoner in this country than in Europe. Italians predominate here, yet they do not have gout in Italy. They may learn new eating or other habits in this country that are conducive to the development of the condition. The difference between gout and the gouty attack was stressed by the speaker. The former is a metabolic disease in which the serum uric acid content is elevated. The latter, on the other hand, is not so clear, and may be dependent on some vasomotor instability. There may be some conditioning factor that explains why certain members of gouty families have attacks whereas others with equally high uric acid concentrations have none. Colchicine is good for the acute episode and should be so, for it has been shown that it exerts its effect on the vascular system. It has no effect on the gout or the uric acid content, although it does diminish the pain. Cinchophen, on the other hand, seems to be better for the gouty constitution and is not too dangerous.

In conclusion, Dr. Talbott stated that in his series the onset of an attack following a particular wine or meat was the exception rather than the rule. In patients studied on a metabolic ward over a period of months, no evidence of any effect of the dietary regimen could be noted. But this should not be construed to mean that patients who have such idiosyncrasies should not stay on a diet. Cinchophen has been found to lower the uric acid levels only intermittently, and nothing has yet been found to lower the values constantly and permanently.

NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine was held in the Bigelow Amphitheater of the Massachusetts General Hospital on January 21.

Dr. T. Stewart Hamilton, assistant director of the hospital, reported on one year's experience in the Physical Therapy Department. A rapid expansion in the use of the department was noted: there was an 87 per cent increase in the number of patients during the first six months. During one year, a total of 2100 patients received 21,266 treatments. The majority (56 per cent) of patients were referred by the Orthopedic Service. The percentages from the other departments were as follows: Medical, 12; Neurological, 10; Skin, 9; Fracture, 6; Surgical, 5; Eye and Ear Infirmary, 1.4; and Psychiatric, 0.6. Attention was called to a lack of understanding by many of the house officers, medical students and staff physicians of the principles of physical therapy and the value derived from its use in many conditions. An educational program has been started to remedy this. At present, a great deal of time and effort is being directed toward emergency training of physical-therapy technicians so urgently needed by army hospitals.

The practice of physical therapy at the Massachusetts General Hospital, as employed in the treatment of some familiar conditions, was described by Dr. A. L. Watkins, director of the Physical Therapy Department. A case of rheumatoid arthritis was presented to illustrate the deformities that may occur when attention is not given to proper orthopedic care and physical therapeutic measures. Prior to entry, this patient developed severe hip and knee flexion contractures and scoliosis in a marked degree. The patient was given bed rest, an adequate diet, and salicylates for control of pain, and the deformities were corrected by balanced leg traction on a Bradford frame. The muscles were strengthened, and the function of joints was regained by supervised therapeutic exercises, at first under water in the Hubbard tub, and later by gait instruction in the walker. Attention was given to postural exercises to improve body mechanics. Local heat to joints in the form of radiant heat lamps, paraffin baths, hot wet packs and diathermy was found helpful in controlling pain, and allowed greater function of involved muscles and joints.

Cases of Bell's facial-nerve paralysis, with early and late recovery, were presented. Patients who did not show a reaction of degeneration usually recovered within three to six weeks regardless of the treatment, whereas with complete nerve degeneration, several months elapsed before beginning function was noted. In these cases, abnormal contractions of all facial muscles occurred, which is described as mass action. This phenomenon was demonstrated by electromyographic recordings. The treatment consisted of splinting, radiant heat, gentle massage, electrical muscle stimulation and graded active symmetrical exercises when possible.

In peripheral-nerve injuries, a test for quantitating the electrical excitability of degenerating and regenerating nerves by means of stimulation by measured condensor discharges was found to be of value in detecting recovery at an early date.

Copper sulfate iontophoresis was used in the treatment of facial pitting and scarring from chronic acne vulgaris, with gratifying results.

The technic of histamine iontophoresis was demonstrated. This measure was useful in producing prolonged local hyperemia for symptomatic relief of muscle pain and spasm in those conditions commonly called "periarticular rheumatism" and "fibromyositis."

Conventional long-wave diathermy has been found to be the treatment of choice in addition to immobilization for nonpurulent sclerosing tenosynovitis. When the acute inflammation has subsided, the whirlpool bath and graded active exercises are started.

The treatment of a compound fracture of the elbow, with radial-nerve involvement, was discussed. This consisted in radiant heat and gentle stroking massage, without elbow motion at first. When bony union permitted, whirlpool bath and guided active exercises of graded intensity were added. The radial-nerve paralysis was followed with electrical and functional tests, which showed spontaneous regeneration. At the end of six months, elbow motion was 80 per cent of normal, with good regeneration of the radial nerve. The patient then started work on the hand loom in the Occupational Therapy Department, to gain further supination and muscle strength and to prepare him psychologically for an early return to work.

An analysis of the types of treatments given during the past year (Table 1) revealed that simpler measures, which are also suitable for home use, constituted approximately 90 per cent of the treatments. More elaborate measures involving electrotherapy constituted the remaining 10 per cent.

TABLE 1. *Analysis of Cases Treated during 1940.*

TYPE OF TREATMENT	NO. OF TREATMENTS	PERCENTAGE OF TOTAL
Radiant heat	9262	22.2
Massage	8661	20.9
Therapeutic exercise	16318	39.3
Hydrotherapy	2680	6.6
Ultraviolet light	1739	4.2
Diathermy	1918	4.6
Electrical stimulation and iontophoresis	926	2.2

The new Physical Therapy and Occupational Therapy departments were opened for inspection at the end of the meeting.

BOOK REVIEWS

Effective Living. By C. E. Turner, A.M., Sc.D., Dr.P.H.; and Elizabeth McHose, B.S., M.A. 8°, cloth, 432 pp., with 164 illustrations. St. Louis: The C. V. Mosby Company, 1941. $1.90.

A textbook for the instruction of school and college classes in the fundamentals of healthful living, this work is based on actual classroom experience, and the material is well organized and adequately presented.

Cardiac Clinics: A Mayo Clinic monograph. By Fredrich A. Willius, M.D., M.S. in Med. 8°, cloth, 276 pp., with 35 illustrations. St. Louis: The C. V. Mosby Company, 1941. $4.00.

Clinics have long been the most popular form of postgraduate education in American medicine because the average physician is more interested in finding out what is being practiced than what is being preached. It is through such teaching clinics that many bits of empirical medical lore are passed along — information that, perhaps, has not been dignified by inclusion in the textbooks. Dr. Willius's volume has been compiled from actual discussions, which have previously appeared in the *Staff Meetings of the Mayo Clinic.* It is perhaps the first book of this type devoted exclusively to heart disease, and it makes very good reading. Examples of all the common etiologic types of heart disease, as well as a number of unusual cases, are included.

Cancer of the Face and Mouth: Diagnosis, treatment, surgical repair. By Vilray P. Blair, M.D., Sherwood Moore, M.D., and Louis T. Byars, M.D. 4°, cloth, 599 pp., with 260 illustrations and 64 plates. St. Louis: The C. V. Mosby Company, 1941. $10.00.

This book is designed to help the practitioner who first sees the patient with cancer of the face and mouth. It emphasizes the need for early recognition of cancer, but places its main stress on the handling of the delayed or recurrent case. Many of the patients presented might be considered incurable, but the results show that even in advanced cases one can achieve brilliant cures by the institution of proper therapy.

The method of destroying cancer about the face and buccal mucosa varies in different clinics. Dr. Blair and his associates frequently use electrosurgical and cautery destruction. A slough is thus formed that clears away and leaves a clean base of granulation tissue. This method has the further advantage of allowing time for the detection of recurrence and its elimination before a plastic procedure is undertaken. In cancers of the tongue, local implantation of radium has been used to the exclusion of surgery in the last ten years. In some cases, surgery was used at a later date to remove a thickening in the scar or early recurrence.

Some will differ with the authors in their selection of treatment for individual cases. Apropos of this is the statement from the text, "It is not so much lack of treatment or poor selection of the kind of treatment that has most handicapped the average recurrent case that we encounter today, but lack of conviction, temporizing methods and halfhearted execution. It is not delayed treatment but puttering treatment that seems to lessen the quality of our average results."

The last part of the work is devoted to a discussion of plastic procedures, half the space being taken up by diagrams of the steps involved. These illustrate the cases discussed in the previous text. By this method, one is kept constantly in touch with the actual case. There is an excellent discussion of neck dissection and radiation therapy in the management of each type of lesion.

Dr. Blair and his group have presented a most difficult problem in a manner that will give immeasurable help to the many surgeons and practitioners throughout the country who treat patients with cancer of the face and mouth.

Wounds and Fractures: A clinical guide to civil and military practice. By H. Winnett Orr, M.D. 4°, cloth, 227 pp. Springfield, Illinois: Charles C Thomas, 1941. $5.00.

The timing of this publication was perfect — dramatically so. In the hands of the author, the results obtained by following the technic outlined may be all that he claims. For situations in which there is such a press of work to be done that timesaving and lack of trained attendants are vital factors, it is conceivable that the method may have advantages. One gets the impression that the author believes that he has introduced something new into the practice of surgery, besides infrequent dressings, when he cites adequate fixation, correction of deformities, overcoming shortening and prevention of, and protection from, infection as the fundamental objects of fracture treatment.

His advice to ignore the existence of shock in determining the time to institute the surgical measures needful to fulfill the above-mentioned cardinal principles of fracture treatment, and the assertion that a little infection in the vicinity of the fracture site may be helpful, on the ground that it might stimulate callus formation provided the wound is well drained, are at least debatable. No well-trained surgeon closes a wound when he has any doubt of its freedom from infection, nor does he dress it more frequently than need be. Plaster-of-Paris fixation, in skillful hands, undoubtedly provides the best security for the fragments. A minimal use of hardware to secure and hold fractures in proper alignment is at times desirable, but to insert a pin indiscriminately in every case, unless it is clear that no other method will suffice, is failing to exercise good judgment, at least in the opinion of the reviewer.

The chapters on the treatment of nerve injuries as a complication of fracture management and on the value of physical therapy are adequate.

The appended bibliography is confined to a list of the author's own writings on the subject of fractures.

X-Ray Therapy of Chronic Arthritis. By Karl Goldhamer, M.D. With a foreword by Harold Swanberg, M.D. 8°, cloth, 131 pp., with 24 original illustrations by the author, 2 roentgenograms and 4 tables. Quincy, Illinois: Radiologic Review Publishing Company, 1941. $2.00.

This small monograph attempts to summarize current knowledge concerning chronic arthritis and experience with its treatment by x-rays. The author, a man of wide roentgenologic experience, has presented with commendable frankness his data in the treatment of 100 patients suffering from chronic arthritis. The drawings of the roentgenologic findings are good but do not show the changes so well as good photographs of x-ray films.

The author believes that x-ray therapy acts on chronic arthritis by stimulating hyperemia and producing improved nutrition in the joint, and also that it produces an analgesia of varying duration. He claims that better results can be expected in the early case than when the arthritis has been present a long time. The technics are described for the various types of arthritis. The reviewer

gained the impression that the author, like many other sponsors of measures of definite value, is somewhat overenthusiastic.

Endocrinology: The glands and their functions. By R. G. Hoskins, Ph.D., M.D. 8°, cloth, 388 pp., with 14 illustrations. New York: W. W. Norton and Company, Incorporated, 1941. $4.00.

It is always difficult to write a book on a scientific subject that will be of value both to the general reader and to the student of the subject. Essentially, this is what the author has undertaken, this work being based on an earlier book, *The Tides of Life*, which appeared in 1933. As Dr. Hoskins states in the preface, "The material has been brought up to date and amplified with an eye particularly to the needs of biologists, psychologists, premedical students and those physicians who desire a not-too-technical introduction to the science of the hormones. I have also tried, however, to keep for the most part within the comprehension of the intelligent general reader." The reviewer believes that there are few general readers with sufficient biologic and medical knowledge to follow the author's discussion with much understanding. For the other group mentioned, it should be very useful.

The author has dedicated the book to "W. B. C." (Walter B. Cannon). After a brief introduction on hormones as chemical regulators, a chapter is devoted to each endocrine gland. There is a chapter on general aspects of endocrinology, such as its relations to the nervous system, the interrelations among the endocrine glands, racial characteristics, endocrine diagnosis and therapy, and endocrine factors in personality. Finally, a short discussion of "Endocrinology of the Future" enumerates some of the unsolved problems of the present that it is hoped will eventually be solved.

The material has been well chosen and clearly presented. Some few statements seem open to question. For example, on page 43, it is stated, "Despite its profound effects in adrenal deficiency, an excess of cortin apparently does no harm." Again, on page 329, the author implies that diabetes is generally treated with a high-fat, minimum carbohydrate diet. But on the whole, the book is most carefully written. There are references at the end of some of the chapters, and a brief general list of sources at the end of the book. A good index is included.

Epilepsy and Cerebral Localization: A Study of the mechanism, treatment and prevention of epileptic seizures. By Wilder Penfield, M.D., D.Sc. (Oxon., Princeton) and Theodore C. Erickson, M.Sc., M.D., with a chapter by Herbert H. Jasper and one by M. R. Harrower-Erickson. 4°, cloth, 623 pp., with 163 illustrations and 17 tables. Springfield, Illinois: Charles C Thomas, 1941. $8.00.

A complete treatise on epilepsy, particularly one that would reflect the vast amount of research on this disease, has long been needed by the medical profession. In recent years, six general books have been published: one in French by Crouzon (1929), one in German by Frisch (1937) and four in English by Lennox and Cobb (1928), Muskens (1928), Jackson (1931) and the extensive and able reports by many investigators issued by the Association for Research in Nervous and Mental Diseases (1931). All these books are at least ten years old, at a time when more knowledge of the treatment of epilepsy has been added to medicine than in any other comparable decade.

It is of interest, moreover, that this book should have come from a neurosurgical clinic, the first to do so, which reflects the importance of surgery in the treatment of the convulsive state. Medical treatment is by no means neglected in this volume, but, as might be expected, the tone is set by surgery: experimental, investigative and therapeutic. Chapters are added on electroencephalography and on psychologic studies of epileptic patients.

The chief sections deal with the history of the disease, seizure patterns, — of which the senior author has been the leading investigator, — cerebral localization of these patterns, epileptogenic lesions, such as scars and tumors, the radical treatment of such lesions, diffuse diseases of the brain with crytogenic epilepsy, and acute head injury. Clearly presented and carefully considered, the material is largely factual and reports, without too wide a generalization, what the authors have seen and reasoned about in their large clinic. This is therefore a personal book, a report of stewardship, largely by Dr. Penfield, who, in training and habit of thought, is eminently fitted to present his findings. That everyone will agree with the amount of surgical therapeutics he uses or with the value of some of his work as a practical form of relief is not to be expected. What is acceptable by the whole profession is a careful study of the epileptic constitution, in which Penfield and his colleagues have had a leading part.

For all who wish to be abreast of the times in the study and treatment of one of the most widespread and disabling of diseases, long an outcast from research, this fine product, in a fitting format, is recommended.

An Introduction to Medical Science. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), F.R.S. (Canada). Second edition, thoroughly revised. 8°, cloth, 358 pp., with 124 illustrations. Philadelphia: Lea and Febiger, 1941. $3.50.

Someone defined the introduction to a book as that part written last, printed first and seldom read. Although such a statement may be true of some books that are written to introduce the reader to a particular art or science, it is not so with this volume, which attempts briefly to encompass medical science and yet contains numerous facts accurately and delightfully recorded. In the second chapter, the author gives a bird's-eye view of the evolution of medical science. In eight pages, he covers the ground from the magic man or the witch man of primitive times to the magic bullets — chemotherapy — of the present day. As on an airplane trip, one visualizes the high peaks on the long journey. This is true of every chapter, and many facts are recorded in an authoritative and attractive manner. Dr. Boyd handles the microscope and the pen with equal dexterity. The following sentence is a striking example: "The gall-bladder has the same nerve supply as the stomach, so that the symptoms of gall-bladder disease are usually referred to the stomach, which seems to cry aloud in sympathy."

This is a book primarily written for nurses. Any nurse who can master all the facts presented will certainly serve in her profession more intelligently. The volume is highly recommended, for it is the product of a person who knows the facts and knows how to present them.

(Notices on page x)